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SOLICITATION OF

THE NATIONAL INSTITUTES OF HEALTH AND

THE CENTERS FOR DISEASE CONTROL

AND PREVENTION

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 8, 2010

Internet: http://grants.nih.gov/grants/funding/sbir.htm

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The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE NATIONAL INSTITUTES OF HEALTH AND THE CENTERS FOR DISEASE CONTROL AND PREVENTION FOR SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PART I INSTRUCTIONS FOR PREPARING AND SUBMITTING A PROPOSAL

1. PROGRAM DESCRIPTION

1.1 PURPOSE OF SOLICITATION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health related topic areas described in Section 12, and to commercialize the results of that R&D, are encouraged to participate.

This solicitation is for Phase I contract proposals and also for Phase I/Phase II Fast-Track contract proposals (see specific topics listed in Section 12 and awarding components identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. **Contract proposals will be accepted only if they respond specifically to a research topic within this solicitation (see Section 12 "Research Topics").** Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR GRANT rather than an SBIR CONTRACT, use the Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Applications (http://grants.nih.gov/grants/guide/pa-files/PA-10-050.html).

The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The Federal SBIR program is authorized under Public Laws 97-219, 99-443, 102-564, and 106-554. The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive, 2002. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components shown in Section 1.3. The guidelines presented in this solicitation reflect the flexibility provided in the Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to the NIH/CDC and to the private sector.

1.2 THREE PHASE PROGRAM

The SBIR program consists of three separate phases:

Phase I: Feasibility; $150,000; 6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further

Federal support in Phase II. Phase I awards normally may not exceed $150,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort; $1,000,000; 2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $1,000,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed two years. *Phase II proposals may only be submitted upon the request of the Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5). Only one Phase II award may result from a single Phase I SBIR contract.*

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the outcomes of the research or R&D funded in Phases I and II. Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR program that improve the health of the American people. In its commitment to also support former President Bush's Executive Order 13329 (http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/pdf/04-4436.pdf), encouraging innovation in manufacturing-related research and development, NIH seeks, through the SBIR program, biomedical research related to advanced processing, manufacturing processes, equipment and systems; or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH Small Business Research Funding Opportunities Web site (http://grants.nih.gov/grants/funding/sbir.htm) and in the NIH Guide for Grants and Contracts (http://grants.nih.gov/grants/guide/index.html) as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers" (http://www.commerce.gov/opa/press/Secretary_Evans/2004_Releases/ManufacturingReport/DOC_MFG_Report_Complete.pdf).

1.3 AWARDING COMPONENTS

The following awarding components are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Center for Complementary and Alternative Medicine (NCCAM)
- National Center for Research Resources (NCRR)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute on Drug Abuse (NIDA)

- National Institute of Environmental Health Sciences (NIEHS)

Centers for Disease Control and Prevention (CDC)

- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

1.4 SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern as defined in Section 3. In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 C.F.R. 121.103, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative, …it does not matter whether control is exercised, so long as the power to control exists." One of the circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 C.F.R. 121.103 also states that control or the power to control exists when "… key employees of one concern organize a new concern … and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise." Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in Section 3 of this solicitation.

If it appears that an offeror does not meet eligibility requirements, the NIH/CDC will request an eligibility determination of the organization from the cognizant SBA Government Contracting Area Office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination.

Project Director/Principal Investigator Criteria. The primary employment of the Project Director/Principal Investigator (PD/PI) must be with the offeror at the time of contract award and during the conduct of the proposed project. The PD/PI is the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the PD/PI's time* is spent in the employ of the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the PD/PI: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. If the PD/PI also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the PD/PI will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the PD/PI is employed by a university, the Dean's Office must provide such a letter. If the PD/PI is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Multiple Principal Investigators. Offerors may propose a multiple Project Director/Principal Investigator (PD/PI) model to direct the project or program to be supported by the contract. The multiple PD/PI model is intended to supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using

the multiple PD/PI versus single PD/PI is the decision of the investigators and their organizations. The decision whether to employ multiple PDs/PIs should be consistent with and justified by the scientific goals of the project.

The offeror organization may designate multiple individuals as principal investigators (PD/PIs) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the offeror organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on a proposal or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

For Multiple PD/PI proposals: The first PI listed must be affiliated with the small business concern organization submitting the proposal and will serve as the **Contact PD/PI**. For both SBIR Phase I and SBIR Phase II, the *primary employment of the "Contact PD/PI" must be with the small business concern at the time of award and during the conduct of the proposed project.*

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see* Part I, Section 3. Definitions*)*.

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project.* It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

Market Research. *The NIH/CDC will not support any market research under the SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable.

For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

2. AGENCY CONTACT FOR INFORMATION

Web Site. The NIH SBIR/STTR Web Site at http://grants.nih.gov/grants/funding/sbir.htm offers electronic access to SBIR solicitations, abstracts of ongoing SBIR projects, the latest updates on the SBIR program, hyperlinks to sources of business assistance, and other useful information.

Technical Questions about Solicitation Topics or Contract Administration. Technical questions about a particular contract topic and general questions on the administration of an SBIR contract should be directed to the appropriate contracting officer listed in Section 10. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

General Questions about the NIH SBIR Program

Ms. Jo Anne Goodnight

NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3540
Bethesda, MD 20892-7963
Phone: 301-435-2688 Fax: 301-480-0146
Email: sbir@od.nih.gov

Ms. Kay Etzler
NIH SBIR/STTR Program Analyst
6705 Rockledge Drive
Rockledge I, Room 3522
Bethesda, MD 20892-7963
Phone: 301-435-2713 Fax: 301-480-0146
Email: sbir@od.nih.gov

General Questions about the CDC SBIR Program

Dr. Paul Smutz
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: 404-639-4783
Fax: 404-639-4903
Email: wsmutz@cdc.gov

Listserv. The NIH maintains a ListServ e-mail broadcast service. To stay in touch with SBIR opportunities and receive notices about upcoming conferences and solicitations, subscribe by sending an email to LISTSERV@LIST.NIH.GOV with the following text in the message body: subscribe listname your name, where listname is the name of the list you wish to subscribe to, and your name is your name. (LISTSERV will get your e-mail address from the "From:" address of your e-mail message.)

3. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 C.F.R. Part 121 – Small Business Size Regulations, §121.103, *"What is affiliation?"*

Autopsy Materials. The use of autopsy materials is governed by applicable Federal, state and local law and is not directly regulated by 45 CFR Part 46.

Child. The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific or ethical reasons not to include them.

DHHS Regulations (45 C.F.R. Part 46, Subpart D, Sec.401-409 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd)) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as research with human subjects that is:
(1) Patient-Oriented Research.
Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded

from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical studies, or (d) development of new technologies.

(2) Epidemiologic and Behavioral Studies.

(3) Outcomes Research and Health Services Research.

Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Coded. With respect to private information or human biological specimens, *coded* means that:

(1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

(2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

Research that involves only coded private information/data or coded human biological specimens may not constitute human subjects research under the DHHS human subjects regulations (45 CFR 46) if:

- the specimens and/or information/data are not obtained from an interaction/intervention with the subject specifically for the research; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited).

Individuals who provide coded information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

(See the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf.)

Commercialization. The process of developing markets and producing and delivering products for sale (whether by the originating party or by others). As used here, commercialization includes both government and private sector markets.

Consultant. An individual who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, grantees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

Contract. An award instrument establishing a binding legal procurement relationship between a funding agency and the recipient, obligating the latter to furnish an end product or service and binding the agency to provide payment therefore.

Data and Safety Monitoring Plan. NIH requires a data and safety monitoring plan for each clinical trial that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the contractor's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Data and Safety Monitoring Board (DSMB). NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, *and generally for Phase III clinical trials*.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one contract proposal or grant application submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Exemptions. The six categories of research exempt from the DHHS human subject regulations are:

> ***Exemption 1:*** Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

Exemption 2: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

(i) information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research with children (see 45 CFR Part 46, Subpart D (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd)), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 3: Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) of the Office of Human Research Protection (OHRP) will determine whether the research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. The NIH Office of Extramural Research website also contains information that is helpful for determining whether human subjects research meets the criteria for Exemption 4. See http://grants.nih.gov/grants/policy/hs/index.htm.

Research that meets the criteria for Exemption 4 is not considered "clinical research" as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research, and targeted/planned enrollment tables, do not apply to research projects covered by Exemption 4.

Exemption 5: Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads and that are designed to study, evaluate, or otherwise examine: (i) public benefit or service programs (ii) procedures for obtaining benefits or services under those programs (iii) possible changes in or alternatives to those programs or procedures or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exemption 6: Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Feasibility. The extent to which a study or project may be done practically and successfully.

Funding Agreement. Any grant, contract, or cooperative agreement entered into between any Federal agency and any small business concern for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

Gender. Refers to the classification of research subjects into either or both of two categories: women and men. In some cases, representation is unknown, because gender composition cannot be accurately determined (e.g., pooled blood samples or stored specimens without gender designation).

Human Subjects. The DHHS regulations "Protection of Human Subjects" (45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm), administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains:

- data through *intervention* or *interaction* with the individual or
- identifiable *private information*

Individually Identifiable Private Information. According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Innovation. Something new or improved, including research for: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For the purposes of PHS programs, an example of "innovation" would be new medical or biological products, for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as "intellectual property," including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR program.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102(f)).

Interaction includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102(f)).

Investigator. The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. (See OHRP's 2004 Coded Specimen Guidance (http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm).)

Joint Venture. An association of concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out a single specific business venture for joint profit, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. A joint venture is viewed as a business entity in determining power to control its management.

For additional information, see http://www.sba.gov/library/cfrs/13cfr121.html.

Manufacturing-related R&D as a result of Executive Order 13329. Encompasses improvements in existing methods or processes, or wholly new processes, machines or systems. Four main areas include:

1. *Unit process level technologies* that create or improve manufacturing processes including:
    - fundamental improvements in existing manufacturing processes that deliver substantial productivity, quality, or environmental benefits.
    - development of new manufacturing processes, including new materials, coatings, methods, and associated practices.

2. *Machine level technologies* that create or improve manufacturing equipment, including:
    - improvements in capital equipment that create increased capability (such as accuracy or repeatability), increased capacity (through productivity improvements or cost reduction), or increased environmental efficiency (safety, energy efficiency, environmental impact).
    - new apparatus and equipment for manufacturing, including additive and subtractive manufacturing, deformation and molding, assembly and test, semiconductor fabrication, and nanotechnology.
3. *Systems level technologies* for innovation in the manufacturing enterprise, including:
    - advances in controls, sensors, networks, and other information technologies that improve the quality and productivity of manufacturing cells, lines, systems, and facilities.
    - innovation in extended enterprise functions critical to manufacturing, such as quality systems, resource management, supply change integration, and distribution, scheduling and tracking.
    - technologies that enable integrated and collaborative product and process development, including computer-aided and expert systems for design, tolerancing, process and materials selection, life-cycle cost estimation, rapid prototyping, and tooling.
4. *Environment or societal level technologies* that improve workforce abilities, productivity, and manufacturing competitiveness, including:
    - technologies for improved workforce health and safety, such as human factors and ergonomics.
    - technologies that aid and improve workforce manufacturing skill and technical excellence, such as educational systems incorporating improved manufacturing knowledge and instructional methods.

Obtains. In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 CFR 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtaining* to include an investigator's use, study, or analysis for research purposes of *identifiable private information* or identifiable specimens already in the possession of the investigator.

Principal Investigator, Program Director, or Project Director (PD/PI). The individual(s) designated by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award. The applicant organization may designate multiple individuals as principal investigators (PDs/PIs) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the applicant organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on an application or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 CFR 46.102(f))

Prototype. A model of something to be further developed and includes designs, protocols, questionnaires, software, and devices.

Research or Research and Development (R/R&D). Any activity that is:

- A systematic, intensive study directed toward greater knowledge or understanding of the subject studied; or

- A systematic study directed specifically toward applying new knowledge to meet a recognized need; or
- A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights a small business concern obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Senior/Key Personnel. The PD/PI and other individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries or compensation are requested under the contract.

Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Senior/Key Personnel. Consultants should also be included if they meet the definition of Senior/Key Personnel. Senior/Key Personnel must devote measurable effort to the project whether or not salaries or compensation are requested--"zero percent" effort or "as needed" are not acceptable levels for those designated as Senior/Key Personnel.

Significant Difference. For purposes of NIH policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Small Business Concern. A concern that, on the date of award for both Phase I and Phase II funding agreements:

1. is organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. is in the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there can be no more than 49 percent participation by business entities in the joint venture;
3. is (i) at least 51 percent owned and controlled by one or more individuals who are citizens of the United States or permanent resident aliens in the United States, (ii) at least 51% owned and controlled by another business concern that is itself at least 51% owned and controlled by individuals who are citizens of, or permanent resident aliens in the United States; or (iii) a joint venture in which each entity to the venture must meet the requirements of either (i) or (ii) of this section;
4. has, including its affiliates, not more than 500 employees.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 C.F.R. 121, as is the process for calculating "number of employees."

Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative. Further information may be obtained by contacting the Small Business Administration Size District Office at http://sba.gov/size.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans;

other groups designated from time to time by the Small Business Administration (SBA) to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. A socially and economically disadvantaged small business concern is one that is at least 51% owned by (a) an Indian tribe or a native Hawaiian organization, or (b) one or more socially and economically disadvantaged individuals; **and** whose management and daily business operations are controlled by one or more socially and economically disadvantaged individuals.

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, territories and possessions of the U.S., Commonwealth of Puerto Rico, Trust Territory of the Pacific Islands, and District of Columbia.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by a woman or women who also control and operate it. "Control" in this context means exercising the power to make policy decisions. "Operate" in this context means being actively involved in the day-to-day management.

4. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

4.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals shall not exceed 50 single-sided, single-spaced pages for the entire proposal, all inclusive [including all pages, cover sheet(s), tables, CVs, resumes, references, pictures/graphics, and all enclosures, appendices or attachments, etc.]. Proposal pages shall be numbered "Page 1 of 50," "Page 2 of 50," and so on. Pages shall be of standard size (8.5" X 11") with a font size of 11 points (or larger). Two sided pages count as two pages. There are NO exclusions to the page limit – the complete proposal shall not exceed 50 pages. Pages in excess of the page limitation will be removed from the proposal and will not be read, considered, or evaluated.

4.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

4.2.1 Technical Proposal Cover Sheet - Complete the form identified as Appendix A (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)), and use it as the first page of the proposal. *No other cover sheet should be used*.

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/PIs), the individual designated as the Contact PI should be entered here.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)
- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.

4.2.2 Abstract of Research Plan - Complete the form identified as Appendix B (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)), and insert it as the second page of each proposal. Do not include any proprietary information as abstracts of successful proposals will be published by NIH. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research.

Include at the end of the Abstract a brief description (two or three sentences) of the relevance of this research to **public** health. In this description, be succinct and use plain language that can be understood by a general, lay audience.

4.2.3 Research Plan

Beginning on page three of the proposal, discuss in the order indicated the following elements:

a. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.

b. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

c. ***Work Plan.*** Provide an explicit, detailed plan for the Phase I R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address how the objectives will be met and the questions stated in Item b above. Discuss in detail the methods to be used to achieve each objective or task. The plan should indicate what is planned, how, when, and where the work will be carried out, a schedule of major events, the final product to be delivered, and the completion date of the effort. The Phase I effort should determine the technical feasibility of the proposed concept. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "Human Subjects Research and Protection from Risk" and the "Human Subjects Research Guidance and Information Supplement."

d. ***Related Research or R&D.*** Describe significant research activities directly related to the proposed effort, including any conducted by the Project Director/Principal Investigator (PD/PI), the proposing firm, consultants, or others. Describe how these activities interface with the proposed project and discuss any planned coordination with outside sources. *The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

e. ***Relationship with Future R&D.***

   1. State the anticipated results of the proposed approach, assuming project success.

   2. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

f. ***Potential Commercial Applications.*** Describe why the proposed project is deemed to have potential commercial applications (for use by the Federal Government and/or private sector markets.) Describe the market as it currently exists and how your product may enter and compete in this market. Include the potential barriers to market entry and how you expect to overcome them.

g. ***Key Personnel and Bibliography of Directly Related Work.*** Identify key personnel, including their directly related education, experience, and bibliographic information. Where resumes are extensive, focus on summaries of the most relevant experience or publications. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Resumes must identify the current or most recent position.

   Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

   If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

h. ***Subcontractors/Consultants.*** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of

two-thirds for Phase I of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

i. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project.* It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

Any research proposal involving the collection of information, such as surveys or interviews, of 10 or more public respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

4.2.4 Current Awards and Pending Proposals/Applications

A small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the NIH/CDC. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award. A firm that receives a Phase I SBIR contract may submit a Phase II grant application and vice versa.

A Phase I contractor may submit a Phase II contract proposal only if invited by an NIH Contracting Officer.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items a-j set forth below.

In addition, provide the information requested in items a-j on (1) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (2) contract proposals and grant and cooperative agreement applications pending review or funding; and (3) contract proposals and grant and cooperative agreement applications about to be submitted.

a. Name and address of the funding source.

b. Type of award (contract, grant, cooperative agreement) and identifying number.

c. Title of research project.

d. Name and title of Principal Investigator(s) or Project Manager(s).

e. Hours per week on the project by the Principal Investigator(s) or Project Manager(s).

f. Annual costs proposed or awarded.

g. Entire period of support.

h. Date of proposal/application submission or date of award.

i. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.

j. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

4.2.5 Prior SBIR Phase II Awards

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II.

This information must be submitted with the proposal.

4.2.6 Proposed Cost Breakdown

Complete the form identified as Appendix C (Contract Pricing Proposal) (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under “Government Solicitation No.,” enter “PHS 2011-1.”
- If supplies are proposed, provide the quantities and the price per unit.
- Under “Direct Labor,” *list all key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- Cost for travel funds must be justified and related to the needs of the project. If travel is proposed, provide the following details on “Exhibit A – Supporting Schedule”: destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement*.
- Use “Exhibit A – Supporting Schedule” to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.
- Small business concerns must perform a minimum of two-thirds of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

4.2.7 Streamlining the Contracting Process

The NIH uses special *"just in time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "just in time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.
- ***Annual Financial Report.*** The offeror's most recent annual financial report.
- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.
- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

4.2.8 Requirement for Adequate Assurance of Protection of Human Subjects

The DHHS regulations for the Protection of Human Subjects, 45 C.F.R. 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. *The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (*http://www.hhs.gov/ohrp*) before a DHHS award can be made.*

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled "**Human Subjects Research**." Place it immediately following the "Research Plan" section of the proposal.

In the Human Subjects Research section, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children.

Provided in the Human Subjects Research Guidance and Information Supplement are six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3 of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, Definitions. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required for IRB review.

4.2.9 Requirement for Adequate Assurance of Compliance with the PHS Policy on Humane Care and Use of Laboratory Animals

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled **"Vertebrate Animals."** Place it immediately following the "Research Plan" section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://grants.nih.gov/ grants/guide/notice-files/NOT-OD-02-064.html).

In August, 2002 NIH announced an IACUC "just-in-time" process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a "just-in-time" fashion prior to award.

The *PHS Policy on Humane Care and Use of Laboratory Animals* requires that offeror organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations

that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 USC 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines “animal” as “any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes.”

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

4.3 LIMITATIONS ON USE OF APPROPRIATED FUNDS

The Department of Health and Human Services Appropriation Act for Fiscal Year 2010 (Public Law 111-117), limits the use of appropriated funds on NIH grant, cooperative agreement, and contract awards for Fiscal Year 2010, as specified below. It is anticipated that these statutory provisions will continue in subsequent fiscal years.

Salary Rate Limitation

Public Law 111-8, Division F, Title II, Section 203 restricts the use of Federal funds to pay the direct salary of an individual under an NIH grant, cooperative agreement, or applicable contract, at a rate in excess of Executive Schedule, Level I of the Federal Executive Pay scale. Direct salary is exclusive of fringe benefits, overhead and general and administrative expenses (also referred to as “indirect cost” or “facilities and administrative (F&A) costs”). Direct salary has the same meaning as the term “institutional base salary.” An individual’s direct salary (or institutional base salary) is the annual compensation that the Contractor pays for an individual’s appointment whether that individual’s time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the Contractor. The salary rate limitation also applies to individuals proposed under subcontracts; however, it does not apply to consultants. The legislation also does not apply to firm fixed price contracts. Effective January 1, 2010, the Executive Level I salary is $199,700 per year. Further information on the NIH Salary Limitation can be found in NIH Guide Notice NOT-OD-10-04 published on January 6, 2010.

Anti-Lobbying

"(a) No part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself. (b) No part of any appropriation contained in this Act shall be used to pay the salary or expenses of any grant or contract recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

Restriction on Distribution of Sterile Needles

"None of the funds contained in this Act may be used to distribute any needle or syringe for the purpose of preventing the spread of blood borne pathogens in any location that has been determined by the local public health or local law enforcement authorities to be inappropriate for such distribution."

Acknowledgment of Federal Funding

"When issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money, all grantees receiving Federal funds included in this Act, including but not limited to State and local governments and recipients of Federal research grants, shall clearly state: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) percentage and dollar amount of the total costs of the project or program that will be financed by non-governmental sources."

Restriction on Abortions

“(a) None of the funds appropriated under this Act, and none of the funds in any trust fund to which funds are appropriated in this Act, shall be expended for any abortion.”

Ban on Funding of Human Embryo Research

“(a) None of the funds made available in this Act may be used for: (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) (2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, the term “human embryo or embryos” includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.”

Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

"(a) None of the funds made available in this Act may be used for any activity that promotes the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established by section 202 of the Controlled Substances Act (21 U.S.C.812). (b) The limitation in subsection (a) shall not apply when there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage."

NIH Public Access Requirement

“The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine’s PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: *Provided*, that the NIH shall implement the policy in a manner consistent with copyright law.”

Further information on the implementation of NIH’s Public Access Requirement is available in NIH Guide Notice NOT-OD-08-033 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html) published on January 11, 2008.

Dissemination of False or Deliberately Misleading Scientific Information

“None of the funds made available in this Act may be used to disseminate scientific information that is deliberately false or misleading.”

While this mandate has not been included in past appropriations acts, it is similar to existing requirements concerning research integrity, fraud, and false claims, and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their implementation of the PHS Policies on Research Misconduct contained in 42 CFR Part 93 and the Civil False Claims Act (31 U.S.C. 3729(a)), Criminal False Claims Act (18 U.S.C. 287 and 1001), and Program Fraud and Civil Remedies Act (31 U.S.C. 3801 et seq.).

Restriction on Employment of Unauthorized Alien Workers

"None of the funds in this Act may be used to employ workers described in section 274A(h)(3) of the Immigration and Nationality Act."

While this mandate has not been included in past appropriations acts, it is similar to existing requirements contained in the Immigration and Nationality Act (18 U.S.C. 1324a), and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their current hiring and employment practices to ensure compliance.

5. "FAST-TRACK" INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The "Fast-Track" initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to Section 12. "Research Topics," for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Phase I and Phase II are considered separate funding agreements under the Fast-Track Initiative. Therefore, Phase I Fast-Track awardees must recertify that they meet all of the eligibility criteria for an SBIR award prior to issuance of the Phase II award.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet, Appendix A (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section 4. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section 7) for Phase I proposals.
2. ***Phase II Proposal.*** Prepared in accordance with Section 6, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section 7) for Phase II proposals.
3. **Commercialization Plan.** Prepared in accordance with instructions in Section 6.2.

The Phase I and Phase II proposals are separate proposals and will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

6. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

6.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals shall not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8.5" x 11") with a font size of 11 points (or larger). Excluded from

the page limitation are cover letters and letters from collaborators and consultants. Pages in excess of the page limitation will be removed from the proposal, and will not be read, considered, or evaluated.

6.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf)).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**
   a. *Detailed Approach and Methodology* - provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in this solicitation.

   b. *Personnel* - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. *Provide resumes for all key staff members,* describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and *provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.*

   c. *Resources* - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. *(Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)*

   d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs Sections 4.2.8 and 4.2.9 of this solicitation for further guidance.

   Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

   If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions, etc.), this must be explained in the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

1. *Data Sharing Plan*: Offerors seeking $500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.). See Data-Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) or http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html.

2. *Sharing Model Organisms*: Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See Sharing Model Organisms Policy (http://grants.nih.gov/grants/policy/model_organism/index.htm), and NIH Guide NOT-OD-04-042 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

3. *Genome Wide Association Studies (GWAS)*: Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088 (http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and http://grants.nih.gov/grants/gwas.

e. *Appendices*

(1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf)). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

(2) **Commercialization Plan** – Required for the Phase II portion of ALL Fast-Track proposals.

The Phase II portion of Fast-Track proposals must include a succinct Commercialization Plan. The Commercialization Plan is limited to *15 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, "Commercialization Plan," and provide a description in each of the following areas:

a. ***Value of the SBIR Project, Expected Outcomes, and Impact.*** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

b. ***Company.*** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will

meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c. ***Market, Customer, and Competition.*** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.

Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (*It is very important that you understand and know the competition*.)

d. ***Intellectual Property (IP) Protection.*** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e. ***Finance Plan.*** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

- Letter of commitment of funding.
- Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
- Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
- Specific steps you are going to take to secure Phase III funding.

f. ***Production and Marketing Plan.*** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g. ***Revenue Stream.*** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or “angels”; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

6. **Summary of Related Activities** - Use Appendix F (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)).

7. **Number of Copies** - Submit an original and 9 copies.

6.3 BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)).
2. **Proposed Cost Breakdown – For Phase I**, use Appendix C (MS Word (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | PDF (http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project. **For Phase II Fast-Track**, use Appendix C. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.
3. **NIH Policy on Threshold for Negotiation of Facilities and Administrative (F&A)/Indirect Costs (IDC) Rates for SBIR proposals** - SBIR offerors who propose in the contract an F&A/IDC rate of 40 percent of total direct costs or less will not be required to provide further justification at the time of award, and F&A/ID costs will be awarded at the requested rate. However, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for F&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) should be used when calculating proposed F&A/ID costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

   SBCs are reminded that only actual F&A/ID costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual F&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS. DFAS will negotiate F&A/IDC rates for SBCs receiving awards if the requested rate is greater than 40 percent of total direct costs.
4. **Number of Copies** - Submit an original and 4 copies.

7. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and Fast-Track proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria in Section 7.1, a panel of scientists, consisting primarily of nongovernment experts knowledgeable in the disciplines or fields under review, will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposal or any specific number of proposals in a given topic. It also may elect to fund several or none of the proposed approaches to the same topic or subtopic.

7.1 EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. When relevant, reviewers will be instructed to comment on the reasonableness of the following Resource Sharing Plans, or the rationale for not sharing the following types of resources. However, reviewers will not factor the proposed resource sharing plan(s) into the determination of scientific merit or priority score. Program staff within the funding organization will be responsible for monitoring the data sharing policy

- Data Sharing Plan [http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]
- Sharing Model Organisms [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html]
- Genome Wide Association Studies (GWAS) [http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html].

The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject

research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component and commercial potential. A Phase I or Fast-Track contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed.*

7.2 TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (Preliminary data are not required for Phase I proposals.)	40%
2. The qualifications of the proposed PDs/PIs, supporting staff, and consultants. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application. The commercial potential of a proposal will be assessed using the following criteria: a. Whether the outcome of the proposed research activity will likely lead to a marketable product or process. b. The offeror's discussion of the potential barriers to entry and the competitive market landscape.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects, (b) commitments of additional investment during Phase II and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	WEIGHT
3. The qualifications of the proposed PDs/PIs, supporting staff and consultants. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	25%
4. The adequacy and suitability of the facilities and research environment.	15%

7.3 PROPOSAL DEBRIEFING

Offerors will be notified promptly in writing if their proposals are no longer being considered for award. Offerors may request a debriefing by submitting a written request to the Contracting Officer within three days of receipt of the notification. Untimely requests may be accommodated at the Government's discretion.

7.4 AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

8. CONSIDERATIONS

8.1 AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Normally, Phase I contracts may not exceed $150,000. Phase II contracts normally may not exceed $1,000,000—including direct costs, indirect costs, and negotiated fixed fee.
5. Cost-sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of your proposal. Cost-sharing is an explicit arrangement under which the contractor bears some of the burden of reasonable, allocable, and allowable contract cost. If cost-sharing is proposed, it should be reflected in your budget summary.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH) National Cancer Institute (NCI)	58	Scientific and Technical Merit Review: March-May 2011 Anticipated Award Date: August-September 2011
National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM)	2-4	Scientific and Technical Merit Review: March 2011 Anticipated Award Date: July 2011
National Institutes of Health (NIH) National Center for Research Resources (NCRR)	4	Scientific and Technical Merit Review: February 2011 Anticipated Award Date: July 2011
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	18-25	Scientific and Technical Merit Review: February-April 2011 Anticipated Award Date: July-September 2011
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	4-8	Scientific and Technical Merit Review: March 2011 Anticipated Award Date: July-August 2011
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	10	Scientific and Technical Merit Review: March 2011 Anticipated Award Date: August 2011
National Institutes of Health (NIH) National Institute of Environmental Health Sciences (NIEHS)	5-8	Scientific and Technical Merit Review: March 2011 Anticipated Award Date: May 2011
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	1	Scientific and Technical Merit Review: May-June 2011 Anticipated Award Date: August 2011
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	1	Scientific and Technical Merit Review: May-June 2011 Anticipated Award Date: August 2011

8.2 MONTHLY PROGRESS REPORT

Contractors will be required to submit monthly progress reports during Phase I along with their invoices. Phase II reports will be required at intervals stipulated in the terms and conditions of award.

8.3 FINAL REPORT

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. **An original and two copies** of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports must be submitted as specified in the contract or as directed by the Contracting Officer.*

8.4 PAYMENT

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the Central Contractor Registration (CCR) database before the award of a contract. The registration site for the CCR is http://www.ccr.gov.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

8.5 LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (DHHS) recognizes that, in responding to this solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the DHHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The DHHS may not be able to withhold data that has been requested pursuant to the FOIA, and the DHHS FOI officials must make that determination. The Government is not liable for disclosure if the DHHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this

solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for Government purposes only.

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (SBC), or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to paragraph (3)of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR program, as described in Section 4 of the SBIR Policy Directive, dated September 24, 2002. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only: (i) Upon expiration of the protection period applicable to the SBIR award, or (ii) by agreement between the awardee and the agency.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: "This publication was made possible by contract number _____ from (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS awarding component)."

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of a patent application.

Inquiries or information about additional requirements imposed by 37 C.F.R. 401 should be obtained from local counsel or from:

Office of Policy for Extramural
Research Administration,
Division of Extramural Inventions and
Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Drive, MSC 7980
Bethesda, MD 20892-7980
Phone: (301) 435-0679

Fax: (301) 480-0272
Email: jpkim@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 USC 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

Awardees are encouraged to submit reports electronically using Interagency Edison (http://www.iedison.gov). Information from these reports is retained by the NIH as confidential and submission does not constitute any public disclosure. Failure to report as described at 37 CFR Section 401.14 is a violation of 35 U.S.C. 202 and may result in loss of the rights of the recipient organization. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via email at Edison@od.nih.gov.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value of, and advance research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions, etc.), this must be explained in the Resource Sharing section of the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

(a) Data Sharing Plan: Investigators seeking $500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.) Offerors are encouraged to discuss data-sharing plans with their program contact. See Data-Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing/) or http://grants.nih.gov/grants/guide/ notice-files/NOT-OD-03-032.html.

(b) Sharing Model Organisms: Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms and related resources, or state appropriate reasons why such sharing is restricted or not possible. See Sharing Model Organisms Policy (lhttp://grants.nih.gov/grants/policy/model_organism/index.htm), and NIH Guide NOT-OD-04-042 (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

(c) Genome Wide Association Studies (GWAS): Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or provide an appropriate explanation why submission to the repository is not possible. A genome-wide association study is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, NIH Guide NOT-OD-07-088 (http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and http://grants.nih.gov/grants/gwas/.

Royalties. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.

2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.
5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).
6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

8.6 PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

For Phase I projects, small business concerns must perform a minimum of two-thirds or 67% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

For Phase II projects, small business concerns must perform a minimum of one-half or 50% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

The Contracting Officer must approve deviations from these requirements in writing after consultation with the agency SBIR Program Manager/Coordinator.

Contractor Commitments. Upon award of a contract, the contractor shall be required to make legal commitments through acceptance of Government contract clauses in the Phase I contract. The outline that follows is illustrative of the types of provisions required by the Federal Acquisition Regulations that shall be included in the Phase I contract. This is not a complete list of provisions to be included in Phase I contracts, nor does it contain specific wording of these clauses. Copies of complete terms and conditions applicable to your contract are available upon request.

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. ***Termination for Convenience.*** The Government may terminate the contract at any time for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.
14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

8.7 ELECTRONIC AND INFORMATION TECHNOLOGY (SECTION 508)

a. Pursuant to Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d), as amended by the Workforce Investment Act of 1998, all electronic and information technology (EIT) products and services developed, acquired, maintained, or used under the resultant contract must comply with the "Electronic and Information Technology Accessibility Provisions" set forth by the Architectural and Transportation Barriers Compliance Board (also referred to as the "Access Board") in 36 CFR part 1194. Information about Section 508 provisions is available at http://www.section508.gov/. The complete text of Section 508 Final provisions can be accessed at http://www.access-board.gov/sec508/provisions.htm.

b. The contractor shall submit electronic reports/documents that meet the requirements of Section 508 of the Rehabilitation Act of 1973, as amended by the Workforce Investment Act of 1998. Conformance shall be verified by producing electronic reports/documents that satisfy the HHS Section 508 Checklists and Standards. (See HHS Section 508 Checklists and Standards) For further guidance, please see http://www.hhs.gov/web/508/index.html.

8.8 ADDITIONAL INFORMATION

1. This solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.
2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.
3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.
4. This solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.
5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I or Phase II.
6. If an award is made pursuant to a proposal submitted in response to this SBIR solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.
7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet at 1-866-705-5711 or via the Internet at https://eupdate.dnb.com/requestoptions/government/ccrreg/. The contractor must also be registered in the

Central Contractor Registry (CCR) prior to award of a contract. Registration can be made via the Internet at http://www.ccr.gov.

9. INSTRUCTIONS FOR PROPOSAL SUBMISSION

9.1 RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:
5:00 p.m., Eastern Time
Monday, November 8, 2010

Any proposal, modification or revision received at the offices designated below after the exact time specified for receipt is "late" and will not be considered unless it is received before award is made, and

1. There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government's control prior to the time set for receipt of offers; or
2. It is the only proposal received.

Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

Proposals may be withdrawn by written notice received at any time before award. Notwithstanding above, a proposal received after the date and time specified for receipt may be considered if it offers significant cost or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

Note: Modifications or revisions to proposals that result in the proposal exceeding the stated page limitations will not be considered.

9.2 NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Fast-Track Phase II, submit the original and 9 copies.

For Phase I and Fast-Track Phase II business proposals, submit an original and 5 copies.

In addition to the paper submissions, proposers are also encouraged to submit two CD-Rom's containing a PDF (Adobe Acrobat) copy of the entire proposal (Technical and Business). This does not replace the paper copies but is in addition to them. The paper copy is the official copy for recording timely receipt of proposals. By signing the proposal, the offeror certifies that, as part of the offer, the information in the paper copy is exactly the same as that which is contained on the electronic media.

9.3 BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

10. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, email, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.

10.1 NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Anita Hughes
Phone: (301) 435-3805
Fax: (301) 480-0309
Email: anita.hughes@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Anita Hughes
Contract Specialist
Office of Acquisitions
National Cancer Institute
6120 Executive Blvd., EPS, Room 6038
Bethesda, MD 20892-7193 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI*.

National Center for Complementary and Alternative Medicine (NCCAM)

Ms. Anita Hughes
Phone: (301) 435-3805
Fax: (301) 480-0309
Email: anita.hughes@nih.gov

Proposals to the NCCAM, if mailed through the U.S. Postal Service, must be addressed as follows:

Ms. Anita Hughes
Contract Specialist
Office of Acquisitions
National Cancer Institute
6120 Executive Blvd., EPS, Room 6038
Bethesda, MD 20892-7193 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to NCCAM*.

National Center for Research Resources (NCRR)

Mr. John Taylor

Phone: (301) 435-0327
Fax: (301) 480-3430
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NCRR, if mailed through the U.S. Postal Service, must be addressed as follows:

Office of Review
National Center for Research Resources
National Institutes of Health, DHHS
6701 Democracy Bl, Room 1072
Room 7091
Bethesda, MD 20892-4874 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NCRR.*

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7195
6701 Rockledge Drive, MSC 7924
Bethesda, MD 20892-7924 *

**Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Mr. Matthew Packard
Phone: (301) 443-3041
Fax: (301) 443-3891
Email: packardm@mail.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Mr. Matthew Packard
Chief, NIAAA Contracts Management Branch
NICHD Office of Acquisitions, NIH
5635 Fishers Lane, Room 3019
Bethesda, MD 20892-9304 *

**Change the city to Rockville, MD and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIAAA.*

National Institute on Drug Abuse (NIDA)

Mr. Brian O'Laughlin
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: bo50d@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Brian O'Laughlin
NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6101 Executive Boulevard
Room 260, MSC 8402
Bethesda, MD 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA*.

National Institute of Environmental Health Sciences (NIEHS)

Ms. Velvet M. Torain
Phone: (919) 541-0400
Fax: (919) 541-2712
Email: torain@niehs.nih.gov

Proposals to the NIEHS must be mailed or delivered to:

Ms. Velvet M. Torain
Supervisory Contract Specialist
Office of Acquisitions, OM
National Institute of Environmental Health Sciences
P.O. Box 12874
Research Triangle Park, NC 27709

Proposals to the NIEHS, *if hand-delivered or delivered by an overnight service*, must be addressed as follows:

Ms. Velvet M. Torain
Supervisory Contract Specialist
Office of Acquisitions, OM
National Institute of Environmental Health Sciences
530 Davis Drive
Research Triangle Park, NC 27709

10.2 CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Dr. Paul Smutz
Office of Extramural Research
Office of the Associate Director for Science
Phone: (404) 639-4783
Fax (404) 639-4903
Email: wsmutz@cdc.gov

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

Theresa Routh-Murphy
Contracting Officer
Phone: (770) 488-2713
Fax: (770) 488-2778
Email: TNR3@cdc.gov

Proposals to the NCCDPHP must be mailed or delivered to:

Theresa Routh-Murphy
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road, MS-E09
Atlanta, GA 30341

National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

Julio Lopez
Contracting Officer
Phone: (770) 488-2892
Fax: (770) 488-2868
Email: jlopez3@cdc.gov

Proposals to NCHHSTP must be mailed or delivered to:

Julio Lopez
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

11. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit http://nnlm.gov/ or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service
1-800-553-6847
http://www.ntis.gov

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
http://www.nttc.edu/

12. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

It is strongly suggested that potential offerors do not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Phase II proposals may only be submitted upon the request of the NCI Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5). Unless the Fast-Track option is specifically allowed as stated within the topic areas below, applicants are requested to submit only Phase I proposals in response to this solicitation.

NCI Phase II Bridge Award

The National Cancer Institute would like to provide notice of a recent funding opportunity entitled the SBIR Phase II Bridge Award. This notice is for informational purposes only and is not a call for Phase II Bridge Award proposals. This informational notice does not commit the government to the development of a Phase II Bridge Award mechanism for, or making such awards to, contract awardees.

Successful transition of SBIR research and technology development into the commercial marketplace is difficult, and SBIR Phase II awardees often encounter significant challenges in navigating the regulatory approval process, raising capital, licensure and production, as they try to advance their projects towards commercialization. The NCI views the SBIR program as a long term effort; thus, in order to help address these difficult issues, the NCI has developed the SBIR Phase II Bridge Award under the grants mechanism. The previously-offered Phase II Bridge Award was designed to provide additional funding of up to $3M and up to three additional years to assist promising small business concerns with the challenges of commercialization. The specific requirements for the previously-offered Phase IIB Bridge Award can be reviewed in the full RFA announcement (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-021.html).

The NCI anticipates expanding the Phase II Bridge Award program in the future to also include awardees funded under the SBIR contract mechanism. Pending its planned continuation, it is anticipated that the Phase II Bridge Award program will be open to contractors who successfully complete a Phase I award as a result of this solicitation, and who are subsequently awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). Provided it is available in the future, NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase II Bridge Award under a future Phase II Bridge Award grant/cooperative agreement funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase II award will be based both on scientific/technical merit as well as business/commercialization potential.

NCI Topics:

This solicitation invites Phase I (and in certain topics Fast-Track) proposals in the following areas:

255 Development of Anticancer Agents

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The short term goal of this SBIR contract topic is to support small businesses that are developing candidate therapeutic agents of interest. The scope of work may include animal efficacy testing, structure activity relationships (SAR), medicinal chemistry, and formulation, production of GMP bulk drug and clinical product, as well as pharmacokinetic, pharmacodynamic, and toxicological studies. These data will establish the rationale for continued development of the experimental therapeutic agent to the point of filing an Investigational New Drug

Application (IND) (http://www.fda.gov/cder/Regulatory/applications/ind_page_1.htm). Successful projects will also be eligible for further development at NCI, including early-stage clinical trials via the Joint DCTD-CCR Early Therapeutic Development Program. Companies should submit proposals for the development of agents that are in mid to late pre-clinical development (expected time to clinic 1-3 years). The development plan, targeted to oncologic indications, will be reviewed by NCI. Agents for rare cancers are of particular interest to the NCI.

Project goals:

The goal of the NCI SBIR program is to accelerate the development of products that benefit cancer patients. The NCI Strategic Plan identifies integrating clinical trial structures to expedite identification of the most promising treatment opportunities and rapid execution of the necessary clinical trials as a strategic priority (Strategy 4.5). Part of this strategy includes creating an integrated infrastructure to accelerate the implementation of high-priority clinical trials. The long term goal of this contract topic is to enable a small business to first bring a fully developed cancer therapeutic agent to the clinic and ultimately to the market.

Phase I activities and expected deliverables:

- Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development.
- Development plan that details the experiments necessary to file an IND or an exploratory IND.
- Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II activities and expected deliverables:

- Complete all experiments according to the development plan (can be re-evaluated if needed).
- If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
- Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance) (http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEProcess/). For additional guidance refer to the following guidance. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078933.pdf).

277 Companion Diagnostics: Predictive and Prognostic Tests Enabling Personalized Medicine in Cancer Therapy

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Recently, the demand for companion diagnostics has greatly increased with the recognition that personalized medicine can improve patient care and may decrease health care costs by bringing specific therapies to individuals more likely to benefit from such treatments. More than a dozen companion diagnostic tests have been approved by the FDA to guide the prescription of products in oncology, cardiovascular disease, and infectious disease. Among them, tests of Philadelphia chromosome, tumor-associated EGFR overexpression, and HER2

protein overexpression have been identified by the FDA as “required” for the identification of candidate cancer patients for receiving Gleevec, Erbitux (cetuximab) and Herceptin (trastuzumab), respectively, in certain indications.

Despite initial success, many therapies in the cancer area are still lacking prediction and guidance from companion diagnostics. In particular, many patients die from recurrence and metastasis as a result of unpredicted drug resistance developed during therapy. Guidance towards effective and safe therapy is therefore much in need. Companion diagnostics include both tests that are developed after a drug has come to market and tests that are being developed in conjunction with the development of a drug. This contract topic seeks to stimulate research, development, and commercialization of innovative tests and technology platforms for both types of companion diagnostics. Companies with advanced biomarkers are particularly encouraged to apply.

Project Goals:

The goal of this contract topic is to develop companion diagnostics for selecting patients for which a particular therapeutic regimen, including existing drugs and those in late clinical development, will be safe and effective. Although the example companion diagnostic tests mentioned above are for targeted therapy, tests may also encompass therapeutics outside of this class. These tests include tumor RNA/protein expression or overexpression, gene mutation or deletion/insertion, allelic variation, and enzymatic deficiency. Noninvasive and minimally invasive sampling methods (e.g., body fluids and mouth swab) are preferred. Other sampling methods are also acceptable if they provide significantly improved predictive value, accuracy, and clinical applicability. This topic is not intended to support the development of assays unless they provide predictive/prognostic information for a therapy. For example, development of an assay for the sole purpose of measuring whether the drug hits its target would not be considered responsive (companies that are interested in developing such assays may wish to look at the alternate contract topic: “Development of Molecular Pharmacodynamic Assays for Targeted Therapies”).

Phase I activities and expected deliverables:

- Develop a working test
- Characterize the variation, reproducibility and accuracy of the test
- Demonstrate suitability of the test for use in the clinic, conduct benchmarking studies against current tests (if available). Algorithms must be tested with datasets other than those used for their development.
- In cases where the drug for which the companion diagnostics being developed is not yet commercially available on the market, the applicant must provide proof of collaboration or partnership with the entity that is developing the therapeutic agent.
- Deliver the SOP of the working test to NCI for evaluation.

Phase II activities and expected deliverables:

- Demonstrate clinical utility and value by testing sufficient numbers of patients to unequivocally prove statistical significance with regards to patient selection for the therapy
- If phase I conclusion is mainly based on animal experiment or ex vivo modeling, then a correlation study between these models and treatment in human subjects may be expected.
- Establish marketing partner or alliance with pharmaceutical companies that are developing the therapy unless the therapy is already on the open market
- Deliver the final SOP to NCI for evaluation.

283 Development of a Molecular Diagnostic Assay to Detect Basal-like Breast Cancer

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 2

Budget (total costs): Phase I: $150,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Breast cancer is a heterogeneous disease with a number of distinct biological entities that are associated with specific morphological/immune-histochemical features and clinical behavior. Basal-like breast cancer is one of the five intrinsic subtypes, which was classified by gene expression profiling in breast cancer. The four other subtypes include luminal A, luminal B, human epidermal growth factor receptor-2 (HER2) over expressing, and normal-like. 15-20% of breast cancer patients have basal-like subtype, which is the most aggressive subtype in breast cancer. It is associated with high grade, poor prognosis, and younger patient age. Population-based study has shown that this subtype is more prevalent in premenopausal African American women, which may contribute to the poor outcomes seen among these patients. Currently there is no effective assay product with low cost to detect the basal-like subtype in the market. The purpose of this initiative is to provide support for the development of a molecular diagnostic assay to detect basal-like breast cancer. The selected proposers will develop an assay for detection of basal-like subtype at the cell, protein, or DNA level. This will enable basal-like breast cancer to be identified specifically. The final assay should enable tests to be completed within one day at a low cost. In Phase I, the development of molecular diagnostic assay should focus on proof-of-concept. In Phase II, the assay developed in Phase I will be validated under a plan developed in consultation with the NCI project officer.

Project Goals:

The goal of the project is to develop an innovative molecular diagnostic assay to detect basal-like breast cancer with the sensitivity and specificity to distinguish basal-like breast cancer from other subtypes in human cells, tissues and body fluids at a low cost. The assay can be used for the early detection of basal-like breast cancer, or as post-treatment monitoring to detect recurrence of the cancer. The assay may also be used to provide a better mechanistic understanding of basal-like tumor development. The knowledge gained will help develop preventive, diagnostic, or therapeutic agents that target specifically against basal-like subtype and further improve patient outcome. The assay development should be platform driven, meaning that the procedure used for the assay development should be easily applied to the development of new assays that detect other cancer subtypes in breast cancer as well as other cancer types such as prostate or colon cancers.

Phase I activities and expected deliverables:

- Identification and validation of a set of markers for the detection of basal like breast cancer.
- Develop an assay to identify these markers effectively and distinguish basal-like subtype from other subtypes in breast cancer with cell lines and/or tissues.
- Demonstration of high reproducibility and accuracy with blinded samples from cell lines and/or tissues
- Demonstration of high specificity and sensitivity of the assay when compared to other subtypes.
- Deliver to NCI the SOPs of the molecular diagnostic assay for basal-like breast cancer.

Phase II activities and expected deliverables:

- Demonstration of the assay that enables a test to be finished within one day.

- Perform studies to characterize the assay in animal models with different subtypes of breast cancer.
- Validation of high throughput screening assays with primary cells and/or tissues obtained from patients.
- Demonstration of platform capability that enables the procedure of the assay development to be easily applied to new assay development for the detection of other subtypes of breast cancer or other cancer types/subtypes.
- Validation of the assay in the clinical setting.
- Submission of regulatory application to obtain necessary approval for clinical validation.

284 Alternative Biospecimen Stabilization and Storage Solutions

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 1-2

Budget (total costs): $150,000 for Phase I for 9 months, $1,000,000 for Phase II for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Current methods for stabilizing tissue specimens for downstream molecular analyses, including freezing and embedding in paraffin, have not undergone significant improvements for many years, are not energy efficient, and require long-term investments in complex and expensive infrastructure. Biorepositories, especially those that store frozen specimens, require significant investments in personnel, space, and sophisticated monitoring and alarm systems to assure that optimal temperatures are maintained. Various dry storage techniques have been developed to provide an alternative to freezing and paraffin embedding, including blood and saliva spot cards. Such techniques have been widely used, for example in the CDC's neonatal screening program. However such methods have not been routinely developed for solid tissue specimens. New approaches are needed that are more universally suited to a variety of tissue types, and maintain the stability of all macromolecules. Such methods should not require hazardous chemicals or expensive equipment and should provide an alternative to the high energy costs required to maintain ultralow temperatures. A method suitable for room temperature storage is preferable. Finally, given the lability of RNA and other macromolecules, stabilization must occur almost immediately after removal from the patient.

Project Goals:

The focus of this contract topic is on the development of novel, innovative, or improved methodology(ies) or reagent(s) for the stabilization and/or storage of cancer tissue biospecimens and their resulting molecular analytes. As discussed in the above section, the NCI is interested in proposals that demonstrate how the product will overcome one of more of the limitations and disadvantages of current biospecimen stabilization and storage methods intended for use in molecular research, namely formalin-fixed paraffin embedded (FFPE) and frozen tissues. The project scope could include reagents and/or novel methodologies for biospecimen fixation, biospecimen storage, and short term post operative biospecimen stabilization for tissue evaluation and/or transport.

The short term goal of this project is the identification and development of a technical strategy with the potential to serve as a useful alternative storage and/or stabilization reagent or method for use by the cancer research community.

The long term goal of this project is to thoroughly test such a method or reagent for effectiveness as a storage and/or stabilization method for cancer biospecimens. Such testing will include evaluating the performance of alternatively fixed/stored biospecimens and analytes against case-matched biospecimens stabilized and stored in

liquid nitrogen or FFPE. Performance evaluation of the product should focus on biospecimen molecular integrity and utility for molecular research platforms.

Offerors should include measurable and quantifiable milestones in regards to the following activities and deliverables:

Phase I activities and expected deliverables: Develop innovative and improved methods or reagents for the stabilization and/or storage of biospecimens and/ or their resulting molecular analytes.

- Demonstrate proof of principle for the development of the reagent or method;
- Provide a description of the technical strategy for the stabilization or storage reagent highlighting the critical operating principles and the experimental design for testing if feasibility has been achieved
- Demonstrate feasibility of use by providing a summary report of results from feasibility testing;
- Test the usefulness of the methods and/or reagent by comparing the outcome of appropriate molecular analysis (dependent on disease and specimen type) with that from matched frozen or FFPE biospecimens;
- Obtain input from potential customers in the research community in preparation for developing a comprehensive commercialization plan for the method or reagent.

Phase II activities and expected deliverables: Refine and analytically validate the reagent or method.

- Provide data comparing the fixation and/or stabilization method and/or reagent to previous widely used methods or reagents detailing performance and any improvements in 1) stabilization of proteins and nucleic acids, 2) quality of biospecimen or resulting analytes for molecular research, 3) general accessibility and ease of use, 4) cost effectiveness compared to FFPE or frozen storage, and 5) hazard level of the involved reagents.
- Demonstrate the use of the method or reagent by stabilizing or storing more than 20 disease matched biospecimens accompanied by matched samples stabilized by FFPE and by freezing, or more than 100 molecular analytes in comparison to all other currently available applicable stabilization and storage methods.
- Provide all comparison data to the NCI
- Generate a scientific publication regarding assay or method performance targeted to the end user audience.

291 Radioprotector/Mitigator Development to Decrease Normal Tissue Injury During Radiotherapy

(Fast-track proposals will be accepted)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Radiotherapy is employed in the treatment of nearly two-thirds of all cancer patients. Many of those patients, however, suffer adverse effects during and/or after treatment. Minimizing normal tissue damage from radiotherapy would improve their quality of life, and may improve tumor control. Several radioprotectors and mitigators that have been developed as potential countermeasures against radiological terrorism have shown promise in that

regard, but for clinical radiation therapy applications it is imperative to demonstrate that those compounds do not protect cancer cells. Ideal compounds would enhance radiation effects on tumors while protecting the normal tissues. According to the operational definitions being adopted in the field, radioprotectors are defined as agents given before radiation exposure to prevent or reduce damage to normal tissues, while mitigators refer to those agents given after radiation exposure but during a patient's prescribed course of radiation therapy to prevent or reduce imminent damage to normal tissues.

The importance of developing agents that protect or mitigate radiation-induced damage, improve survival, quality of life, and palliative care in cancer patients was emphasized in a recent NCI conducted workshop on NIH Advanced Radiation Therapeutics - Radiation Injury Mitigation held on January 25th 2010. Several small businesses participated in the workshop, which underscored their significant interest in this area as well as the great potential for collaborations between small businesses and academic clinical sites to develop and clinically evaluate the proposed agents. The report from a previous NCI-sponsored workshop conducted in 2003 to develop approaches to prophylaxis, mitigation, and treatment of radiation injuries is referenced here (Stone, H B et al, Models for Evaluating Agents Intended for the Prophylaxis, Mitigation and Treatment of Radiation Injuries Report of an NCI Workshop, December 3–4, 2003).

This contract topic is to encourage the development of innovative and promising radioprotectants/mitigators that selectively protect normal tissues (but not tumors) against ionizing radiation, thereby increasing the therapeutic ratio. Proposals are solicited that include preclinical and/or early phase clinical studies demonstrating safety, efficacy, dose, schedule, pharmacokinetics (PK), pharmacodynamics (PD), and metabolism. Proposals should also demonstrate a clear understanding of regulatory requirements, and should include a regulatory plan including key steps such as a pre-IND meeting with FDA, submitting an investigational new drug (IND) application, approval of clinical trial design, and ultimately drug registration.

Project goals:

The goal is for collaborations among academic institutions, small businesses, and contract research organizations to lead to the rapid development of innovative radioprotectors/mitigators that will decrease normal tissue injury and subsequently improve radiotherapy. The long-term goal is to enable small businesses to fully develop, license, and/or market radioprotectors/mitigators.

The contract proposal must describe:

Phase I:

- A quantitative estimate of the patient population that will benefit from the availability of such radioprotectants/mitigators
- A plan for generating evidence that the proposed compound(s) protects at least one relevant normal tissue from radiation-induced injury.
- A plan for generating evidence that the proposed compound(s) does not significantly protect cancer cells and, if applicable, evidence of its anti-cancer effects.
- The methodology proposed to evaluate the preferential protection of normal tissues by the compound(s) *in vivo* (including appropriate biomarkers and endpoints as determined during early interactions with the FDA).
- Determination of the optimum dose and schedule *in vivo* based upon preclinical pharmacodynamic and pharmacokinetic studies.

Phase II:

- The approach to early-phase human trials, as indicated, that are designed taking into account the relevant molecular pathways and targets and which aim to gather pharmacodynamic and pharmacokinetic data to confirm the compound's observed behavior in animal studies.

- The approach to assessing the safety and efficacy of the compound(s) in early-phase human trials employing, as appropriate, physician-reported endpoints as well as patient-reported outcomes.

Deliverables:

Phase I may include primarily preclinical studies. Phase II or "Fast-Track" proposals must contain a section entitled "Regulatory Plan" detailing plans for early involvement of the FDA. There should be a description of how the applicant plans on meeting these requirements to determine suitable biomarkers and endpoints, filing IND and design for performance of phase 0-2 clinical trials allowing product transition ready for phase 3 clinical trials by groups such as the RTOG. Where cooperation of other partners is critical for implementation of the proposed methodology, the applicant should provide evidence of such cooperation (through partnering arrangement, letters of support, etc.).

The following deliverables may be required depending on a compound's maturity in the developmental pipeline:

Phase I:

- Selection and approval of cell panels for *in vitro* testing.
- Demonstration of drug solubility and uptake using cultured normal and transformed cells.
- Study design for determining clonogenic survival tailored to the mechanism of each tested compound.
- Clonogenic survival data validating lack of drug toxicity in normal cells, efficacy and specificity of radioprotection for normal cells. Preliminary evidence for lack of *in vivo* toxicity.
- Documentation providing a top-level description of the protocols and the testing results should be provided to NCI as part of the Phase I progress report

Phase II:

For advanced pre-clinical work:

- Design an NCI/institutional animal care and use committee approval of *in vivo* experimentation plan. In addition, selection and approval of tumor cell panel and normal tissues for *in vitro* testing.
- Demonstration of lead compound(s) bioavailability PK and PD in rodent model.
- Demonstration by physiologic testing and histological assessment of irradiated normal tissue sparing over a 6-month period.
- Demonstration of effects on tumors using *in vivo* radiation regrowth delay assays
- Collection of data validating lack of drug toxicity, efficacy, and specificity for normal cells over tumor cells.

For proposals advancing to early phase human trials:

- GMP drug source
- IND approval
- Evidence of established clinical collaboration
- Protocol submitted for IRB approval
- Definition of suitable objective and patient-oriented outcomes

Documentation of the testing protocol and testing results should be provided to NCI as part of the Phase II progress report for pre-clinical studies.

292 Development of Molecular Pharmacodynamic Assays for Targeted Therapies

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3

Budget (total costs): Phase I: $150,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The NCI requests that qualified small businesses submit proposals to develop assays of pharmacodynamic (PD) protein biomarkers identified by NCI for the measurement of the drug response to a number of high-priority molecular targets. Real-time assays to rapidly assess the response to treatment in the early clinical trial setting are highly desirable. The primary goal of this contract topic is to develop new, robust, and validated assays to measure molecular-level responses to treatment in conjunction with the development of new candidate therapeutic agents. These assays will be used in animal models and on human tumor and surrogate tissue samples provided by NCI. Ideally, assay measurements should correspond to tumor modulation via the same target as in animal efficacy models. Company deliverables are standard operating procedures (SOPs) for the assays, all supporting data, and critical reagents and instrumentation for independent validation (if applicable). (To view sample SOPs, please see http://sbir.cancer.gov/funding/contracts/.)

Ideally, the NCI will assist selected SBIR offerors in the development of robust PD assays for immediate clinical use via collaboration and partnership. An example of this collaboration is provision of relevant drug-treated xenograft tumor tissue for the target of interest for Phase I 'fit-for-purpose' demonstration, and if agreed upon for Phase II, provision of surrogate clinical specimens and bulk critical reagents, calibrators, and positive and negative controls generated in NCI's laboratories and GMP grade–like contracting and manufacturing facilities. The provision of high-quality assay kit components and appropriate specimens for 'fit-for-purpose' determinations is essential for ensuring successful validation of the assay in Phase 1 and II development. Furthermore, once successfully transferred these assays will undergo clinical "fit-for-purpose" studies in NCI Phase 0/I clinical trials, which may lead to the generation of FDA-quality data for 510k or PMA market approval. The clinical demonstration of assay performance is often critical to capture market share through widespread clinical adoption, as well as for obtaining coverage by health care insurers. Although the type of partnership/collaboration will be unique for each assay, the NCI will be able to assist the company defray some of the costs and can leverage NCI resources to accelerate the timeline for assay development and generation of data required for CLIA laboratory adoption and/or FDA approval.

Discovery of new PD biomarkers will not be considered and the application will be considered 'unresponsive', and therefore, will not be reviewed.

Project goal:

To develop a series of CLIA-quality, analytically validated molecular PD assays to previously identified biomarkers to confirm clinical target modulation for a wide array of cancer therapeutics. These assays will be used for early determination of whether a target is modulated as intended by a therapeutic agent. The deliverables for the contract recipient are written SOPs; supporting data, including analytical validation and fit-for-purpose testing results using surrogate models in Phase I (cell lines and xenograft tumors) and surrogate clinical specimens in Phase II; and critical reagents and instrumentation (if applicable) for independent validation.

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute. It is expected that companies will extend this work into developing research kits or evaluating dosing and target modulation of new therapeutic agents. The NCI Strategic Plan identifies validating molecular targets for cancer prognosis, metastasis, treatment response, and cancer progression as a strategic priority (Strategy 4.2). This Strategy also includes creating a library of validated molecular target assays to advance broad development of targeted anti-tumor agents. Grant mechanisms have

not been an effective method, thus far, of developing these assays as they have little publication value. Market analysis indicates that CLIA-quality PD assay development, qualified critical reagents, and fit-for-purpose target modulation are valuable steps for eventual commercialization of laboratory assays, in addition to advancing cancer therapeutic development.

Phase I Activities and Expected Deliverables:

- Develop an analytically validated, PD research assay of specified biomarkers (listed below) using qualified critical reagents for the molecular target(s) described. Critical reagents include antibodies, calibrations, controls, and if applicable detection systems.
- Characterize assay reproducibility, variability, and accuracy.
- Demonstrate “fit-for-purpose” target modulation in appropriate models (cell lines and drug-treated tumor biopsy samples provided by NCI). A list of existing models and inventory of frozen tumor biopsies will be provided. New models and target pathway inhibitor treatment will require a 3 month notification prior to delivery.
- Deliver to NCI the SOP(s) for the PD research assay of the molecular target(s) described, and all supporting data.
- Make available to NCI sufficient critical reagents (for 100 assay runs) and instrumentation (if applicable) for independent evaluation.

Phase II Activities and Expected Deliverables:

- Develop validated, CLIA-quality, target-specific PD assays using bulk, qualified critical reagents (≥3 lots) including a robust calibrator.
- The assay should be ready for late-stage assay development activities to include full assay transfer, clinical validation, and NCI clinical trial support.
- Determine if analyte(s) can be successfully measured with the assay in minimally invasive surrogate tissues (e.g., peripheral blood mononuclear cells, skin, hair follicle, and/or blood samples provided by NCI).
- Determine optimal specimen procedures.
- Perform studies to characterize the correlation between the resulting assay in representative human versus animal tumors (specimens possibly provided by NCI).
- Deliver to NCI the SOP(s) for the CLIA-quality PD assay for the molecular target(s), successful specimen SOP(s), and all supporting data.
- Make available to NCI sufficient critical reagents (100 assay runs) and instrumentation (if applicable) for independent evaluation.
- Determine next steps for kit generation.

Molecular Pharmacodynamic Targets of Interest to NCI

The following molecular pharmacodynamic targets and/or platforms/instrumentation have been identified as high priority for the NCI based on the current pipeline of therapeutic agents. This list of identified molecular targets is being actively pursued by NCI researchers; assays developed under this topic will therefore be good candidates for beta testing at NCI laboratories and clinics. The NCI will determine and periodically re-prioritize the list of molecular targets to be addressed based on the needs of both intramural and extramural investigators:

1. Multiplexed assays for obtaining multiple, integrated PD readouts from a single tumor biopsy specimen (any technology platform, e.g., microscopy, immunoassay of laser capture micro dissected tissue, etc).
    a. Interrogate multiple targets within a molecular pathway, such as PTEN/Akt/PI3K/mTORC1 & 2; Wnt/ Frizzled; Notch/Jagged/gamma-secretase; SHH/Smoothened/Gli; or NF-kappaB/IKK.
    b. Interrogate across multiple core signaling pathways of human cancer types identified by genome-wide analyses, pathway module signatures, or other types of global analyses of the cancer genome. For example, the 12 core pathways identified in pancreatic cancer (see Jones et al., *Science* 321, 1801 [2008]) or the three core pathways identified in glioma (see The Cancer Genome Atlas Research Network, *Nature* 455, 1061 [2008]).
2. Multichannel quantitative slide-based immunofluorescence, infrared, and far infrared microscopy assays with companion image analysis methods, and other tissue visualization methods for difficult PD evaluations in biopsy specimens, for example:
    a. Identification of tumor stem cells using specific monoclonal antibodies to 3 or more stem cell markers on a single slide, e.g., ALDH 1A1, SOX2, OCT 3/4, NANOG, CD44v6, CD133, CD166, CD49b, Olfm4, and/or innovative stem cell markers already established scientifically by the company.
    b. Restricted PD evaluation of 2 or more PD endpoints to tumor stem cells identified by multiple markers.
    c. Restricted PD evaluation of cell surface receptor tyrosine kinases to the plasma membrane compartment.
    d. Restricted PD evaluation of nuclear markers to the inner nuclear membrane.
    e. Quantitative evaluation of low-prevalence molecular targets (~5,000-10,000 molecules per cell) against the backdrop of high-prevalence targets (~100,000-1,000,000 molecules per cell).
3. Assays for quantifying important phosphorylated sites on members of the Met proto-oncogene family other than Met, and/or their specific enzymatic products (e.g., STK, SEA).
4. Assays for quantifying new nuclear markers that are early indicators of apoptotic commitment of tumor cells, preferably using slide-based immunofluorescence, although other assay formats will be considered.

Sample Standard Operating Procedures (SOPs):

As mentioned above, sample Standard Operating Procedures (SOPs) are available at http://sbir.cancer.gov/funding/contracts/. They demonstrate the level of rigor expected for pharmacodynamic assay development activities under this contract topic. They do not indicate a preference for a particular technology platform.

293 Development of Devices for Point of Care Analysis of Circulating Tumor Cells

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Circulating tumor cells (CTCs) are cancer cells that shed from either the primary tumor or its metastases and then circulate in the peripheral blood. While metastases are directly responsible for the majority of cancer deaths,

CTCs may constitute seeds for metastases and may be instrumental for the spread of the disease. Therefore the development of CTC-related applications is very important.

Analysis of CTCs may allow earlier detection of metastasis-capable malignancy when it is in a less invasive stage, and the ability to remove CTCs from circulation could potentially limit metastases after surgery. Many studies have shown that the presence of CTCs in peripheral blood and/or bone marrow is of prognostic significance in different types of solid tumors, and that CTC numbers also help to monitor treatment response. The current FDA-approved CTC analysis is based on immunological capture of CTC by magnetic beads. However, this method does not capture all types of CTCs and may be limited in its efficiency and accuracy. Hence, it is important to develop improved methodologies for CTC detection, enumeration, isolation, and subsequent genetic or proteomic analysis. Moreover, the development of technologies that allow the efficient removal of CTCs from the circulation could have therapeutic potential. This contract topic seeks to stimulate research, development, and commercialization of innovative devices and methodologies designed for Point of Care (POC) analysis of CTC-based diagnostics and prognosis.

Project Goals:

The long-term goal of the project is to develop Point of Care (POC) devices and methods of CTC detection, enumeration, isolation, removal and subsequent genetic and proteomic analysis for better cancer diagnosis, prognosis and treatment. The major focus is to develop clinical tools rather than tools for basic research. In the long term, these tools should be developed as POC devices and must perform at a lower cost than current methodology or must offer significantly improved sensitivities/specificities or new features such as predictive diagnostics or treatment management tools not available with current technologies. The short term goal is to demonstrate the technical viability of the proposed approach to detect and/or isolate and/or eliminate CTCs in an experimental setting. Acceptable studies include:

- CTC isolation and enrichment technologies such as magnetic separation, microfluidics, size separation and negative or positive selection.
- Surface antigen based CTC isolation and analysis
- Viable CTC cell isolation and/or culturing for treatment assessment
- Scanning, imaging, flow cytometry technologies for CTC
- Technologies to predict treatment and to monitor progress using CTCs
- Non-separation based technologies for CTC
- Other tools for CTC detection, enumeration, isolation and analysis with clinical utilities.

Phase I Activities And Expected Deliverables:

- Demonstrate the feasibility of the innovation (e.g. spiking relevant body fluids with CTCs and perform experiments with a bench-top device). Conduct benchmarking studies against current technologies (if available)
- Characterize the variation, reproducibility, and accuracy of the method
- Provide NCI with detailed estimations of the cost for producing the proposed devices and/or reagents, including an analysis/breakdown of vendors and/or sources of raw materials

Phase II Activities And Expected Deliverables:

- Develop a prototype of the POC device incorporating the technology demonstrated in Phase I
- Test with a sufficient number of patient samples to demonstrate clinical utility and advantages, with an appropriate consideration of statistical significance

- If CTC elimination devices are developed, they should also be tested with in vivo animal models

294 Development of Glycosylation-Specific Research Reagents (Antibodies and Aptamers)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: $150,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The availability of site-specific antibodies that recognize phosphorylation sites in proteins has been a tremendous resource for basic cancer researchers. It has revolutionized the field of signal transduction, and has had a significant impact on our understanding of cancer cell physiology and regulation. The carbohydrate modification O-GlcNAc is nearly as abundant as protein phosphorylation in proteins, competes with it, and has extensive crosstalk to regulate signaling, transcription, and the functions of oncogenes and tumor suppressors. However, analysis of protein O-GlcNAcylation currently requires difficult and time-consuming methods such as sophisticated mass spectrometry. There is a need to develop new reagents and simpler methods to study the function of carbohydrate modifications (O-linked and N-linked) of proteins in cancer biology.

Even in labs with the ability to make glycosylation-specific antibodies, it is simply too time-consuming and expensive to do that on a scale which would have an impact on the field. Currently, there are hundreds of O-GlcNAc sites on critical regulatory proteins like p53, c-myc, estrogen receptors, etc. The availability of site-specific O-GlcNAc antibodies (imaging reagents) would cause an explosion of work to improve understanding of the effects of glycosylation events during carcinogenesis, and would allow investigators to conduct many productive studies using simple analysis methods like western blotting. Similarly, we know that N-linked glycosylation in proteins is also critically important in cancer biology, so production of antibody reagents with binding specificities for N-linked carbohydrate modifications in proteins is also needed.

Project Goals:

The long-term goal of this contract topic is to develop new research reagents for basic cancer researchers in the form of antibodies or aptamers against N- or O-linked carbohydrate antigens in proteins. These antibodies or RNA/DNA aptamers will be used as reagents to enable functional and imaging studies of the role of carbohydrate modifications in cancer signal transduction processes. There is an immediate need for 20 to 100 cancer-relevant, carbohydrate-specific laboratory reagents that would make it possible to delineate differentially glycosylated proteins and to jump-start the study of oncoprotein regulation by glycosylation.

Phase I Activities And Expected Deliverables:

- Chose cancer-relevant antigen(s) and specific peptide(s)
- Develop antibody or aptamer production system
- Express and purify reagents
- Perform preliminary reagent characterization, including testing binding specificity

Phase II Activities and Expected Deliverables:

- Validate reagent extensively for specificity, purity, and reproducible use in three assay types:
    - Immunoprecipitation assays

  - Western blot
  - Immunohistochemistry assay
- Scale up production (milligram quantity) of purified reagent
- Deliver to NCI the optimized production and purification protocols
- Develop and test prototype detection kits/reagent packages for commercialization

295 Algorithms for Automated Quantitative Imaging of Tumor Microenvironment

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2

Budget (total costs): Phase I: $150,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The range of phenotypes which arise from a single genotype and from multiple genetic variations, environmental exposures, gene-gene interactions and gene-environment interactions are intricate phenomena. These variations may significantly impact the tumor microenvironment (in and around a tumor). This microenvironment plays a significant role in tumor initiation, promotion, and control. Spatiotemporal differences in endogenous and exogenous toxicant and carcinogen levels in the tumor microenvironment may significantly influence the expressed phenotype. Harnessing the vast amounts of information from genetic screens (single nucleotide polymorphisms, copy number variations, and genomic instability) and integrating that information with high throughput phenotyping of the tumor microenvironment should speed up functional annotation of genetic and epigenetic variants. By employing immunohistochemistry/microscopy, hundreds of molecular and morphological features can be obtained in a single screen in order to characterize the interactions and understand the role of the microenvironment in cancer. Machine learning techniques can be used to find combinations of those features that can classify complex phenotypes (subclinical, intermediate, and severe phenotypes).

At present, the biggest bottleneck in high-throughput phenotyping is digital image data analysis. The two-dimensional (2D) digital images captured during the screening, compressed sensing technologies for image processing, and the histological reconstruction of 3D images using the 2D images can generate terabytes and petabytes of data. Current automated imaging and data analysis algorithms take several hours to days to process, and often require human intervention. The increasing amount of digital information requires the development of next generation automated imaging systems and analytical tools. These tools should enable the completion of analyses in a few hours with little or no human intervention for the interpretation of histological features. In addition to facilitating characterization of the tumor microenvironment and its role in cancer, these tools may be useful for functional annotation of genetic variants, and for clinical diagnosis at the point of care.

Applicants to this topic are encouraged to explore the Network for Translational Research (NTR; http://imaging.cancer.gov/programsandresources/specializedinitiatives/ntroi) or Quantitative Imaging Network (PAR-08-225), which conducts translational research in imaging.

Project Goals:

The primary goal of this topic is to encourage small businesses to develop automated high-throughput technologies for imaging that will enable investigators to diagnose, characterize, and grade both the tumor and its microenvironment. The technologies should be automated for the interpretation of captured images and should require little or no human intervention.

Examples of novel technologies and approaches that might be developed in response to this topic include the following: image analysis algorithms for differential diagnosis of histological subtypes of cancer; multiplexing of tumor markers for bright-field, fluorescent, and/or luminescent visualization; robotics and algorithms for automated image capture, histological reconstruction, biomarker quantitation, and differential diagnosis. Offerors are encouraged to develop appropriate innovative technologies to meet the goals of this contract topic. Technologies and approaches aimed at characterizing the tumor microenvironment are of particular interest to NCI.

Phase I activities and expected deliverables:

- Development of algorithms that are fast and efficient in image segmentation, incorporate pattern, multicolor (multiple biomarkers), hue and luminosity parameters to obtain both qualitative and quantitative measures, and require less storage and computing space.
- Show marker-independent and marker-dependent automated analyses of the tumor microenvironment for automated differential analysis of histological subtypes.
- Validation and demonstration of accurate automated interpretation of “hot spots” based on morphological and molecular pattern recognition.

Phase II activities and expected deliverables:

- Application and optimization of technique(s) to analyze microscopic images of human tumor tissues.
- Adaptation of techniques for automated qualitative and quantitative analyses of digital images for high-throughput screening of cancer biospecimens.
- Development of commercially viable technologies that is capable of differentiating complex histological phenotypes.

296 Systems for Automated Storage, Analysis, and Reporting of Objective Behavioral Exposures

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Over the past decade, there have been rapid advancements in the technology and methods used to objectively measure behavioral exposures in clinical and research settings. Leading examples include accelerometer-based devices used to assess physical activity and sleep within remote clinical monitoring or research applications. Additional biological sensors (such as electrocardiography), as well as advances in mobile imaging-based dietary intake assessment, offer further opportunities to objectively measure behavioral exposures. With the advent of electronic medical records and the focus on the epidemic of obesity and related co-morbidities, clinicians, researchers, and practitioners are increasingly interested in utilizing objective measures to monitor patient/participant behavior as a tool for chronic disease prevention or management and health research.

Accelerometer technology is now commercially available that can generate and store unfiltered movement data during physical activity and sleep for post-processing. This offers an advance over proprietary sensors for behavioral assessment and will allow for standardized data processing to generate behavioral measures for clinical practice and research. However, software systems necessary for managing and analyzing the unfiltered data collected by these sensors are currently unavailable. The complexity of data management and analysis needed to generate objective behavioral measures from existing technologies presents a significant barrier to the

integration of these measures into clinical practice and trials, epidemiological research, and bio-repositories. Objective exposure measures within these settings offer tremendous potential to increase the understanding of the relationships of behavioral exposures and gene-environment interactions with risk of chronic diseases including cancer. In order to overcome current barriers and facilitate integration of objective behavioral measures into applications including electronic medical records and other health information systems, contracts shall stimulate development of an easily deployable architecture for data collection, storage, analysis, and reporting of behavioral bio-signals.

Project objectives include:

1) Development of a standardized database architecture to capture and store objective behavioral measures or biosignals
2) Development of open source non-proprietary analytic tools to generate individual and/or group level behavioral measure summary outputs
3) Development of output reporting systems to communicate outputs to patients/subjects, electronic medical records, health surveillance systems, or researchers

Project Goals:

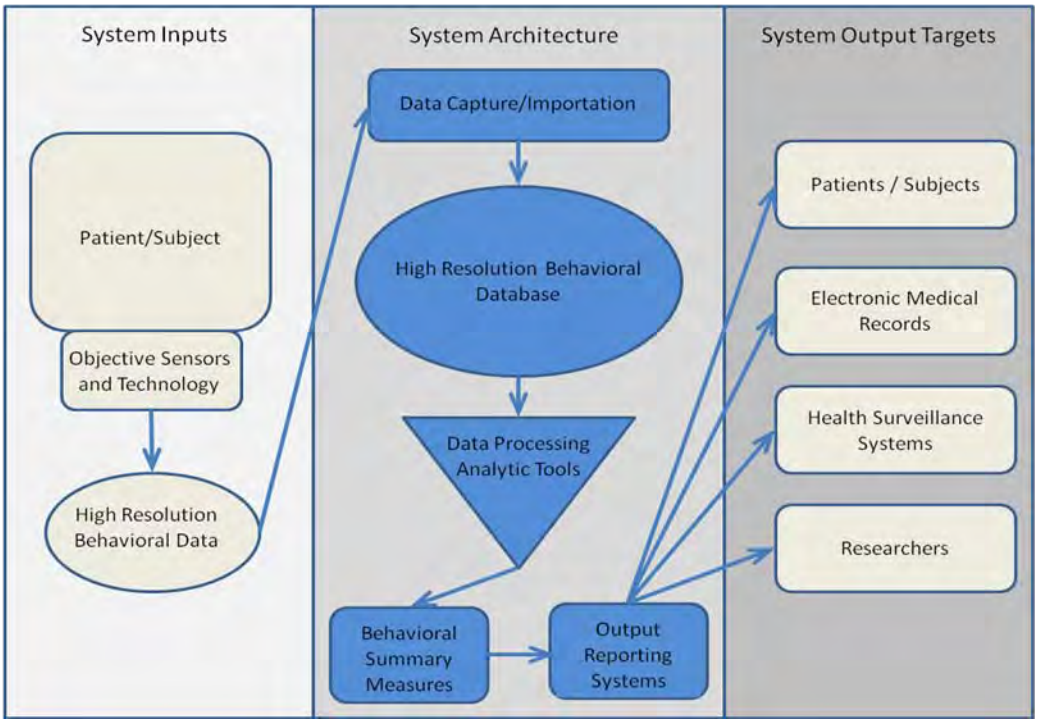
This topic addresses the need for development of high throughput, low time cost methods to standardize behavioral data outputs (e.g. physical activity) for use in clinical and research settings, and for case management in prevention or treatment of chronic disease. This topic's goal is to encourage development of software systems and tools for data capture or importation, storage, analysis, and output reporting of objective behavioral measures. Proposals are encouraged from software developers regardless of device manufacturing capability. Priority behavioral measures include physical activity and sleep. Priority sensors for these measures include accelerometers capable of collection and storage of unfiltered high resolution motion data or targeted signal characteristics (e.g., characteristics of acceleration waveform) suitable for advanced analytic methods under development, including signal processing and pattern recognition algorithms. Capacity to incorporate or expand to handle additional health related biosignals or objective dietary data is also encouraged, such as data from mobile electronic food diaries or food images. The NIH Genes, Environment and Health Initiative (GEI) Exposure Biology Program has supported development of sensor technology and analytic methods for objective behavioral exposures with relevance to the current topic.

Proposals must demonstrate full cycle capacity from data capture/importation to behavioral output reporting (where existing analytic methods allow for tools development). Standardized methods to directly capture data or import electronic data files from objective monitoring technologies for health behaviors shall be utilized to generate a structured database for raw/unprocessed behavioral measures. An essential task for each proposal is the development of transparent non-proprietary and expandable analytic tools to generate summary person or group level behavioral measures. Although valid methods are required, proposals are not required to include the calibration or validation of data processing methods for behavioral research. Data processing applications and analytic tools may be drawn from established or emerging methods for bio-behavioral data/signals processing research and practice. Proposals must demonstrate development of data standards and capacity for sharing behavioral summary measures via output reporting systems. Recommended short term targets for behavioral outputs include capacity to provide reports to patients/participants, health systems, and researchers. Long-term, the goal is to provide reports directly to electronic medical records and public health surveillance systems. Recommended output reports are consistent with current health outcomes policy priorities and objectives in the Meaningful Use Matrix for electronic health records established by the Health Information Technology Policy Committee. (See http://healthit.hhs.gov/portal/server.pt.)

Figure 1 summarizes data flow through the system considering a high resolution data stream collected with an accelerometer-based physical activity monitor. A patient wears a triaxial accelerometer that stores unfiltered movement data in three axes at 40Hz for one week. The device will generate approximately 24 million lines and 3 columns of raw motion data plus columns for time and other measures. The developed system shall be capable of capturing/importing and storing the raw sensor output for this participant within a behavioral database for analysis and archiving. An expandable set of analytic tools for such physical activity input data shall be developed. The tools may use available validated analytic signal processing methods. Physical activity summary measures such

as active and sedentary bout patterns, posture and activity classification and time allocations, and associated energy expenditure may be generated and stored. Finally, summary measures would be reported directly to the patient and transmitted to the patient's electronic medical records for review and follow-up by health care team members.

Figure 1. Schematic of data cycle architecture to enable objective behavioral data collection, storage, analysis, and reporting in clinical and research applications



Phase I Activities and Expected Deliverables:

- Establish a project team including expertise in behavioral science, objective technologies for behavioral assessment, advanced behavioral data/signals processing methods, and database and computational systems that will effectively address all aspects of the current topic.
- Provide a report including detailed description and/or technical documentation of the proposed:
  - database structure
  - data standards for capture and storage of instrument data
  - expected sensor/technology compatibility matrix
  - data linkages to identify person and group level data characteristics
- Develop a functional prototype system that includes a database structure/repository capable of direct data capture or data importation from compatible sensors, instruments, or imaging devices with a user interface (web- or computer-based).
- Provide a report detailing planned analytic tools and resulting system capabilities for behavioral summary data outputs. The analytic tools plan shall include justification for the algorithm source(s) selected or to be developed.
- Provide a report detailing output reporting systems feasibility, proposed timelines, data standards, and communication architecture for reporting behavioral outputs to patients/subjects, electronic medical records, health surveillance systems, and researchers.

- Finalize system user-interface, database formats, repository structure, and data capture/importation methods for targeted data inputs.
- Include funds in budget to present phase I findings and demonstrate the final prototype to an NCI evaluation panel.

Phase II Activities and Expected Deliverables:

- Develop, beta test, and finalize analytic tools listed in phase I.
- Develop, beta test, and finalize applicable user interface systems.
- Develop and beta test output reporting systems' capabilities for multiple system output targets listed above.
- Demonstrate system compatibility with devices included in the phase I compatibility matrix.
- Develop systems documentation where applicable.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

297 Methods and Tools for Quantitatively Measuring Non-Coding RNAs in Cancer Early Detection, Prediction, and Diagnosis

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 2-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Accurately detecting preneoplastic lesions and early cancer, distinguishing benign diseases from precancerous lesions, and predicting cancer progression, can dramatically improve cancer treatment and prevention. To achieve this goal, it is crucial to discover novel molecular markers that could perform better than or complement current cancer detection technology, such as imaging. For molecular markers to be clinically useful, it is essential to develop technologies, methods, and assays to precisely detect and quantitatively measure these novel biomarkers.

Noncoding RNAs (ncRNAs) are recently-discovered molecules that have shown promising potential for the early detection and diagnosis of cancer. NcRNAs, which include long ncRNA and ultra conserved regions encoding ncRNAs, do not code for proteins, but they are biologically functional transcripts that regulate transcription, translation, and development. The majority of ncRNAs are microRNAs (miRNAs), which have been demonstrated as promising cancer biomarkers because of their unique properties: The expression patterns of miRNAs in human cancers appear to be tissue specific; miRNAs are stable in human body fluids of plasma and serum; and they can be used to classify poorly differentiated tumors. These molecular characteristics have demonstrated that using miRNAs as molecular markers for cancer early detection and diagnosis holds significant potential. While miRNAs have been discovered as promising biomarkers for cancer early detection, there is an absence of developed technology and methods which could be used to precisely measuring miRNAs and other ncRNAs. Therefore, it is urgently needed to develop and improve technologies and assays to precisely detect and quantitatively measure ncRNAs.

Project Goals:

The overall goals of this SBIR/STTR contract topic are to encourage eligible small businesses to develop innovative or improved technologies and tools that detect and quantitatively measure miRNAs and other ncRNAs for cancer early detection, diagnosis, and prediction of progression from preneoplastic lesions to cancer. To avoid internal competition between projects and encourage diversity of scientific approaches for ncRNA detection, program funds will be used to support companies focusing on detection of a limited set of cancers (1 or 2). Short-term goals are to develop proof-of-concept in developing high-throughput technologies and tools to quantitatively measure miRNAs and other ncRNAs in body fluids and/or in those specimens with small numbers of cells. Any type of specimen can be used for technology development, provided that the ncRNAs being detected are present at physiological concentrations. Long term goals are to commercialize these technologies for molecular diagnosis of cancer. Examples of proposals include:

- High throughput ncRNA profiling assays
- Biosensor-based methods for detecting and measuring ncRNAs
- Chemistry- based technologies to detect ncRNAs
- Nanotechnology-based technologies for measuring ncRNAs
- Novel methods and probes for detecting ncRNA molecules inside living cells
- Novel ncRNA nanoparticles and imaging assays
- NcRNAs, including miRNAs microarrays with better sensitivity and specificity than currently available ones
- Methods for profiling and quantifying long ncRNA or miRNA expression
- Multiplex real-time polymerase chain reaction (RT-RCR) assays for ncRNAs

Phase I Activities and Expected Deliverables:

1) Design novel ncRNA methods/assays or improve existing technologies that could be used to detecting and quantitatively measuring ncRNAs in physiological concentrations for cancer early detection, diagnosis, and prediction.
2) Deliver a prototype method or assay for profiling ncRNAs, including miRNAs and/or multiplex assays, such as RT-ncRNAs.
3) Use specimens, such as body fluids, serum, plasma, and urine, from 10 cancer patients and 10 healthy individuals to simultaneously and quantitatively measure 10 to 15 miRNAs/ncRNAs with the developed technology. These 10-15 miRNAs/ncRNAs could be selected from literature. It is highly encouraged to select miRNAs/ncRNAs that have shown a clear association with cancer in previous studies.
4) Deliver protocol, software, and instructions for proposed technology and for multiplex assays for profiling and validating miRNAs and other ncRNAs.
5) Deliver the initial results, particularly from # 3 to NCI program scientists for evaluation prior to Phase II development.

Phase II Activities and Expected Deliverables:

1) Refine the tools and methods developed in Phase I; perform analytical validation to test accuracy and reproducibility.
2) Determine the validity and utility of ncRNAs in tumors and body fluids to provide a basis for developing noninvasive assays for early diagnosis.

3) Use the tools to test and validate 30 ncRNAs that have shown the potential for cancer biomarkers and/or to perform genome wide profiling of ncRNAs.
4) Validate the methods using clinical samples.
5) Generate instruments, kits and software that could be used for high throughput assays.
6) Plan the commercialization of the tools and methods as well as relevant kits, reagents, and services.

298 Low-Field Electron Paramagnetic Resonance Imaging Device to Optimize Development of Anti-Angiogenic Therapeutics in Cancer Animal Models (NIH TT)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The commercial availability of a device to measure tissue oximetry non-invasively would have important and direct implications for the development of anti-cancer therapeutics. Over the last decade, one of the most promising classes of anti-cancer agents has been anti-angiogenic agents. According to the NCI, anti-angiogenic agents are now being tested in active Phase III treatment trials against 14 types of human cancer. A necessary component of preclinical analysis of candidate anti-angiogenic therapeutics is measuring the efficacy of the drugs in tumor-bearing animal models. Currently, the effects of candidate drugs are discerned primarily through volumetric changes in the tumor that typically require weeks to occur and thus consume highly valuable time. In contrast, the subject inventions enable quantitative *in vivo* measurement of drug-induced neo-vascular suppression. This invention would dramatically cut down the time currently required to identify and measure anti-angiogenic effects, thus speeding the development time of these drugs to commercialization, and ultimately to the patient's bedside.

Electron Paramagnetic Resonance Imaging (EPRI) is a form of Magnetic Resonance Imaging (MRI) that has recently been recognized as an important tool for noninvasive imaging of tissue oxygen pressure (pO_2). One important potential application of EPRI is the *in vivo* screening of candidate anti-angiogenic drugs in mouse models of human cancer through observation of drug-induced neo-vascular suppression. However, for *in vivo* imaging, current EPRI technologies are not suitable because it is difficult to design and construct resonant cavities large enough and having the required shapes. Second, motion, including respiration and heartbeat, can alter the resonance frequency. Finally, as most microwave energy is absorbed in the first few centimeters of tissue, it is impossible to obtain adequate signal strength for imaging at greater depth. To overcome these obstacles, it is necessary to use lower resonance frequencies.

The NCI Center for Cancer Research (CCR) has developed two inventions that may address this shortcoming. One invention is a low-frequency coil design suitable for detecting time domain electron paramagnetic resonance responses from spin probes after low frequency, irradiation-mediated pulse excitation. The design can accommodate and irradiate objects of varying dimensions containing free radical spin probes and induce an EPR signal that can also be recovered by a resonator. Such a resonator has the capability of facilitating the enhanced dissipation of noise to thermal noise levels associated with the input power from the radio-frequency pulse, and recovering weak and rapidly- decaying free induction decays. This invention is fully described in U.S. Patent Number 5,865,746 and is the subject of HHS Reference Number E-175-1995/0.

A second invention is an image-formation method for *in vivo* imaging of physiological function. It emphasizes image resolution and quantitative assessment of *in vivo* tissue oxygen. The method pertains exclusively to time-domain Fourier Transform EPR imaging (FT-EPRI) with emphasis on spatial and temporal resolution. This

invention is fully described in PCT Patent Application Number PCT/US2009/65956 and is the subject of HHS Reference Number E-250-2008/0.

Project Goals:

The ultimate goal of this topic is to develop a commercial scanner that employs the algorithms developed by the CCR inventors for *in vivo* imaging of physiological functions, such as tissue oxygen status. The development of this technology would aid in optimizing development of anti-angiogenic cancer therapeutics. The short term goal of this project is to develop a functional prototype capable of generating oxygen-related physiological maps using the described inventions.

This is an NIH TT (Technology Transfer) contract topic from the NCI. This is a new program whereby inventions from the NCI Intramural Research Program (Center for Cancer Research, CCR) are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract topic shall work closely with the NCI CCR inventor of this technology, who will provide access to operational scanners and hardware as well as image-formation and reconstruction algorithms. The inventor will provide assistance in a collaborative manner with reagents and discussions during the entire award period. Between the time this contract topic is published and the time an offeror submits a contract proposal for this topic, no contact will be allowed between the offeror and the NCI CCR inventor. However, a pre-submission public briefing and/or webinar will be given by NCI staff to explain in greater detail the technical and licensing aspects of this program (for further information, see http://sbir.cancer.gov/news/upcoming/). In addition, a list of relevant technical, invention, and licensing-related questions and answers (including those from the public briefing) will be posted, maintained, and updated online (http://sbir.cancer.gov/news/upcoming/) during this time period.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor can apply for an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. Offerors submitting an SBIR contract proposal in response to this topic are strongly encouraged to submit concurrently an application for a commercialization license to such background inventions. Under the NCI NIH TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

To apply for an exclusive commercial license to develop this NIH invention, an SBIR offeror or SBIR contractor must submit a license application to the NIH Licensing and Patenting Manager: Michael Shmilovich, shmilovm@mail.nih.gov or (301) 435-5019. A license application and model license agreements are available at http://www.ott.nih.gov/pdfs/LicApp.pdf and http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#LAP.

This license application provides NIH with information about the potential licensee, some of the terms desired, and the potential licensee's plans for development and/or commercialization of the invention. License applications will be treated in accordance with Federal patent licensing regulations as provided in 37 CFR Part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5.

Phase I activities and expected deliverables:

- Build a transmit channel capable of pulsed excitation with 10-100 nanosecond pulses to provide broad band excitation of an object the size of a mouse.
- Build a resonator having short recovery time after an input power at 300 MHz sufficient to study a mouse in a 25 x 25 mm coil.

- Build a receive system comprising a preamplifier and digitizer/averager module.
- Assemble the transmit channel, resonator, and receive system into a prototype.
- Perform phantom testing on the prototype with an external magnet, evaluate the sensitivity and resolution of the images generated, and test oximetry.

Phase II activities and expected deliverables:

A Phase II proposal will typically/generally only be invited by NCI if the Phase I contractor has been granted a commercialization license via the NIH license application process described above. Phase II envisages the development of a *complete pulsed EPR imaging system with all the necessary modules explicitly outlined below and conforming to the precise specs mentioned.* This will involve definite and defined improvement over the Phase I prototype. The end product will be a stand-alone research EPR imaging spectrometer ready for application in testing anti-angiogenic drugs using appropriate mouse models.

- Based on the prototype built in Phase I, build a device with an internal magnet. Build a magnet/gradient assembly with homogeneity better than 50 ppm at an operating field of 10 milliTesla over a 5 cm diameter spherical volume. This should be a 3-axis gradient system capable of providing gradients of a maximum of 30 milliTesla/meter with linearity better than one percent (1%).
- Build a versatile pulse programmer with time resolution better than one (1) nanosecond, capable of generating the desired pulse shapes/sequences including pseudo-random noise (stochastic) excitation, Frank pulse sequences, and spin echo sequences.
- Build a receive system with recovery times less than 200 nanoseconds from the coil and the front end preamplifiers.
- Build a data acquisition system with sampling/summing rates and a bit resolution of better than 10 bits.
- Integrate image-formation and reconstruction algorithms.
- Design, optimize, and conduct testing in cancer animal models of image resolution, and tissue oximetry. Test the effect on tissue oximetry and tumor volume of at least three FDA-approved anti-angiogenic agents (e.g. Avastin, Sutent, Nexvar).
- Provide a letter of interest from a pharmaceutical company to use the EPR technology/device to screen for new anti-angiogenic drugs in animals
- Provide to NCI the Standard Operating Procedure for evaluation in animals of the effect on tissue oximetry of known anti-angiogenic drugs
- Provide a letter of commitment from a pharmaceutical company to use the EPR technology/device to screen for new anti-angiogenic drugs in animals

299 A New Type of Vaccine for Prevention of HIV Infection and HIV-Associated Cancers (NIH TT)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $300,000 for 9 months; Phase II: $2,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

An HIV vaccine would have important and direct implications in our fight against AIDS and many types of cancer. HIV infection weakens the immune system and the body's ability to eliminate abnormal cells, which can lead to cancers. HIV infection increases the risk for Kaposi sarcoma about 800-fold, Hodgkin lymphoma at least 10-fold, anal cancer at least 9-fold, non-Hodgkin lymphoma at least 7-fold, liver and lung cancer 3-4 fold, and, among women, cervical cancer at least 3-fold. Further, people that are co-infected with HIV and other viruses (for example, Human herpesvirus 8, Epstein Barr virus, Human papillomavirus, and Hepatitis B virus) are at an increased risk for cancers associated with those secondary viruses.

Despite more than two decades of intense research, only several broadly neutralizing anti-HIV-1 antibodies (bnAbs) have been identified and characterized. However, attempts to clinically elicit these antibodies, or antibodies that target the same epitopes, have failed. It is now known that these mature bnAbs are highly divergent from their putative predecessor germline antibodies. Recently, it was demonstrated that putative germline predecessors of some of these bnAbs do not bind to HIV-1 envelope glycoproteins (Envs). This and other findings indicate that currently used vaccine immunogens may not be capable of initiating immune responses leading to elicitation of bnAbs.

The NCI Center for Cancer Research (CCR) has developed a new technology whereby a primary immunogen can activate B cells that express putative germline predecessors of previously identified bnAbs. The inventor and his associates have identified one antigen that can bind a putative germline-like precursor of a known anti-HIV-1 bnAb. This invention is fully described in PCT Patent Publication Number WO/2010/042919 and is the subject of U.S. Patent Application Number PCT/US2009/060303 and HHS Reference Number E-322-2008/0.

Using this technology, possibly in combination with other not-yet-identified primary immunogens and probably in combination with Env-based immunogens, it may be possible to elicit bnAbs in a clinical setting. Necessary innovations include discovery of additional primary immunogens and *in vivo* immunogenic analyses of all primary immunogens using an appropriate animal model. Potentially necessary innovations include identification of intermediate B cells (intermediate in the maturation pathway of the mature bnAb) and the discovery/*in vivo* analyses of immunogens for these intermediate B cells.

Project Goals:

The ultimate goal of this topic is to accelerate the development of efficacious vaccines that can activate bnAb precursor germline B-cells and elicit anti-HIV-1 bnAbs. The short term goals of this topic are to test the *in vivo* immunogenic potential of the identified potential primary HIV immunogen in an innovative animal model and identify, and similarly analyze, one or more candidate primary immunogens. A mouse with human germline antibodies is an appropriate animal model to use.

This is an NIH TT (Technology Transfer) contract topic from the NCI. This is a new program whereby inventions from the NCI Intramural Research Program (Center for Cancer Research, CCR) are licensed to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this contract topic shall work closely with the NCI CCR inventor of this technology, who will provide putative germline predecessors of an anti-HIV bnAb, at least one candidate primary immunogen, mature bnAbs, Env-based putative immunogens, control antibodies, cell lines, reagents for binding and neutralization assays, as well as other reagents as needed. The inventor will provide assistance in a collaborative manner with reagents and discussions during the entire award period. Between the time this contract topic is published and the time an offeror submits a contract proposal for this topic, no contact will be allowed between the offeror and the NCI CCR inventor. However, a pre-submission public briefing and/or webinar will be given by NCI staff to explain in greater detail the technical and licensing aspects of this program (for further information, see http://sbir.cancer.gov/news/upcoming/). In addition, a list of relevant technical, invention, and licensing-related questions and answers (including those from the public briefing) will be posted, maintained, and updated online (http://sbir.cancer.gov/news/upcoming/) during this time period.

The awarded contractor will automatically be granted a royalty-free, non-exclusive license to use NIH-owned and patented background inventions only within the scope and term of the award. However, an SBIR offeror or SBIR contractor can apply for an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention. Offerors submitting an SBIR contract proposal in

response to this topic are strongly encouraged to submit concurrently an application for a commercialization license to such background inventions. Under the NCI NIH TT program, the SBIR contract award process will be conducted in parallel with, but distinct from, the review of any applications for a commercialization license.

To apply for an exclusive or non-exclusive commercialization license to develop this NIH invention, an SBIR offeror or SBIR contractor must submit a license application to the NIH Licensing and Patenting Manager: Sally Hu, Ph.D., HuS@mail.nih.gov or (301) 435-5606. A license application and model license agreements are available at http://www.ott.nih.gov/pdfs/LicApp.pdf and http://www.ott.nih.gov/forms_model_agreements/forms_model_agreements.aspx#LAP. Certain terms of the model license agreement are subject to negotiation. Please contact Dr. Hu with further questions.

This license application provides NIH with information about the potential licensee, some of the terms desired, and the potential licensee's plans for development and/or commercialization of the invention. License applications will be treated in accordance with Federal patent licensing regulations as provided in 37 CFR Part 404. A further description of the NIH licensing process is available at http://www.ott.nih.gov/licensing_royalties/intra_techlic.aspx. NIH will notify an SBIR offeror or SBIR contractor who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 8.5

Phase I activities and expected deliverables:

- Characterize *in vitro* the already identified putative primary immunogen for binding to human germline antibodies.
- Identify novel potential primary immunogens of bnAbs against HIV using putative germline predecessors of bnAbs.
- Perform *in vitro* characterization of the newly identified primary immunogens for binding to human germline antibodies.
- Obtain or generate and maintain mice that carry human germline antibody genes and that can be used as an *in vivo* model, e.g., can elicit high-affinity human antibodies by immunization.

Phase II activities and expected deliverables:

A Phase II proposal will typically/generally only be invited by NCI if the Phase I contractor has been granted a commercialization license via the NIH license application process described above.

- Analyze the immunogenic potential of the identified candidate primary immunogens in combination HIV envelope glycoprotein (Env)-based immunogens in the mouse animal model from Phase I.
- Characterize the antibody response elicited by the combination of primary immunogens and Env-based immunogens. Specifically, measure the binding titer of the serum against the immunogens used for immunization, and the neutralization titer of the serum against a panel of HIV-1 primary isolates from different clades provided by the inventor. Also isolate monoclonal antibodies at several time points, sequence them, analyze them in terms of somatic mutations and maturation stage, and characterize their binding to the immunogens used for immunization.
- Optimize immunization protocols and adjuvants for elicitation of antibodies with increased potency and breadth of neutralization.
- Provide optimized Standard Operating Procedure for immunization to the NCI.
- Recommend immunogens for further preclinical development based on their capability to elicit bnAbs. If this goal is not achieved, recommend immunogens for further research and development based on their

ability to elicit antibodies that are intermediates in the maturation pathways of known bnAbs, providing a proof-of-concept for this approach.

- If this goal is achieved perform preclinical research in preparation for human phase I clinical trial.

300 Therapeutics and Theranostics Based on Nanotechnology

(Fast-track proposals will be accepted.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Nanoscale devices carrying therapeutic payloads and delivered within close proximity of the tumor *in vivo* can play a significant role in increasing the effectiveness of the treatment while decreasing severity of side effects. Such techniques would be highly relevant, particularly, for organs that are difficult to access because of a variety of biological barriers, including those developed by tumors. For example, nanoparticles are capable of crossing the blood-brain barrier due to their small size and thus are an excellent candidate for the non-invasive treatment of brain tumors.

Multifunctional nanoscale devices, which are currently emerging, allow for a combination of a diagnostic agent with a therapeutic and even a reporter of therapeutic efficacy in the same nanodevice package. In conjunction with the development of these devices, local targeting techniques are also emerging. This process can utilize epitopes expressed on the surface of tumor cells or other cellular markers of biological processes such as angiogenic and apoptotic pathways. In molecular oncology, it allows for the targeting of multiple cancers or even more broadly for targeting of multiple diseases. For instance, there are already examples of multi-functional nanoparticles that target vascular peptides, growth factor receptors, transmembrane proteins such as ion channels, and are utilized for both cancer and cardiovascular disease recognition.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based multifunctional therapeutic or theranostic (combination of diagnostic and therapeutic capabilities) structures.

Project Goals:

The goal of this project is to demonstrate an *in vivo* nanodevice-based platform which provides improved efficacy of treatment or improved treatment combined with diagnosis in one construct (theranostic). These devices can take, for example, the form of multi-functional targeted nanoparticles or multi-chamber chips carrying encapsulated drugs. Further, the devices may also utilize imaging agents for a combination of therapeutic and diagnostic modalities that aim to provide real-time feedback and monitoring of therapy. The devices operating in vivo can be administered orally, intravenously, or can be implanted. They may include the following:

- novel therapeutic nanodevices
- novel theranostic nanodevices capable of diagnosing and subsequently treating cancer
- devices involving novel tumor targeting and concentrations schemes
- novel theranostic nanodevices which contain both a therapeutic agent and a reporter of tumor environment (e.g., pH, hypoxia, necrosis, vascular collapse)
- novel drug loading and releasing schemes

- novel therapeutic or theranostic nanodevices which are able to cross the blood-brain barrier
- novel nanodevices which predict the tumor response to a particular therapeutic agent prior to the administration of the therapeutic agent (i.e., a predictor of efficacy)
- novel therapeutic or theranostic devices which are implantable

Phase I activities and expected deliverables:

- proof-of-concept small animal studies showing improved therapeutic efficacy as compared to the use of free drug (at least 60 day study with statistically relevant number of animals) utilizing an appropriate animal model
- demonstration of simultaneous diagnosis and treatment in small animal models for theranostic devices
- manufacturing techniques resulting in the manufacturing of nanodevices with good reproducibility should be developed. The novel use of existing particles acquired from the commercial manufacturer will also be considered under this program

Phase II activities and expected deliverables:

- long term toxicity studies (biodistribution and bioelimination for IV administered nanodevices and biocompatibility for implanted devices)
- if the construct use active targeting, side-by-side comparison of targeting effectiveness for targeted and non-targeted approaches
- demonstration of nanodevice manufacturing and scale-up scheme
- IND-enabling studies carried out in a suitable pre-clinical environment
- initiation of large animal studies

301 Nanotechnology Sensing Platforms for Improved Diagnosis of Cancer

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Nanotechnology allows for the design and manufacture of complex multi-functional devices which could lead to the miniaturization of biological assays. Current diagnostic assays require a patient visit to a physician's office or travel to a laboratory. Nanotechnology-based devices and instruments hold the potential for point-of-care applications in which assays could be conducted by the primary care physician in their office or by the patient in their home as well as by health care workers in remote geographical locations or in hospitals for bed-ridden patients. Additionally, these systems will require much smaller volumes of sample for analysis than conventional assays thus reducing the cost associated with reagents and the time required for conducting of some of these assays (e.g., heating and cooling in PCR-based assays).

For several types of cancer, the primary cause of poor survival is late detection, almost always after the disease has spread to distant sites. For example, most melanomas that are found without evidence of metastasis can be cured with surgical resection. In contrast, for the patients with advanced or metastatic melanoma, the prognosis is

poor (a 5-year survival of 5-10%). Consequently, efforts are currently being made to develop new early-stage diagnostic solutions relying on highly sensitive and specific assays and the use of prognostic biomarkers.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based diagnostic platforms that will ultimately assist and improve current clinical protocols of cancer detection and diagnosis as well as post-therapy monitoring.

Project Goals:

The goal of the project is to develop nano-enabled diagnostic platforms that can provide increased sensitivity and specificity in recognizing cancer that would ultimately offer clinicians a way to maximize the chance of early disease recognition and positive clinical outcomes. The platforms can be used for early detection of initial onset of disease, or be used as post-treatment monitoring to monitor effectiveness of treatment and to detect recurrence of disease. Strategies can also include screening assays that provide a better understanding and prediction of metastasis which can help develop better therapies and further improve patient outcome.

Potential relevant sensing nanoplatforms could include:

Nano-enabled Sensing Platforms for in vitro Applications

Examples: Use of functionalized nanomaterials (nanowires, nanotubes, nano-cantilevers, etc.) to develop diagnostic platforms monitoring presence of biological signatures specific to one or more cancers.

Potential Applications: Novel platforms that would 1) enhance sensitivity/specificity of existing candidate biomarker detection and validation; or 2) allow for monitoring of disease recurrence; or 3) for detection, isolation and/or characterization of circulating tumor cells (CTCs).

Nano-enabled Sensing Platforms for in vivo Applications

Examples: Use of functionalized nanomaterials introduced into patient organism and subsequently collected for *ex vivo* evaluation of biochemical, metabolic and/or pharmacological data regarding tumor status or therapeutic efficacy.

Potential Applications: Long-term monitoring of treatment effectiveness, determination of therapeutic efficacy, monitoring of tumor metastasis.

High throughput Screening Nanoplatforms

Examples: Nanotechnology-based devices for highly parallel, high throughput assay development.

Applications: Identifying and detecting novel cancer biomarkers that may be undetectable using traditional assays; detecting cellular changes using nano-sensors to screen for novel therapeutic agents.

Given the diversity of potential applications discussed above, submitted proposals should place emphasis on the specific nanotechnology-enabling component of the proposed platform.

Phase I Activities and Expected Deliverables

- Design describing:
    - unique temporal capabilities enabled by nanotechnology
    - proof of concept experiments
    - benchmarking experiments against conventional methodologies
- First-stage validation of design in relevant preclinical samples,
    - *In vitro* sensing platforms: Demonstrate identification of candidate biomarkers in bodily fluid samples (e.g., blood, urine, saliva, semen, etc.) containing artificially elevated concentrations of candidate

biomarkers (i.e., "spiked" samples) with the sensitivity better than 100 picomoles; demonstrate identification or isolation of CTCs from bodily fluids containing artificially elevated concentrations of CTCs (i.e., "spiked" samples) with sensitivity better than 10 cells per milliliter

- o *In vivo* sensing platforms: Demonstrate identification of candidate biomarkers in bodily fluid samples (e.g., blood, urine, saliva, semen, etc.) containing artificially elevated concentrations of candidate biomarkers (i.e., "spiked" samples) with the sensitivity better than 100 picomoles
- o High throughput screening assays: Validate device using subcultured cell lines and/or frozen tissue samples

- Successful completion of benchmarking experiments demonstrating a minimum of 5x improvement against conventional methodologies

Phase II Activities and Expected Deliverables

- Second-stage validation of design for potential clinical adaptation
  - o *In vitro* sensing platforms: Demonstrate identification of candidate biomarkers in clinical samples from cancer patients (bodily fluids or tissue) with the sensitivity better than 100 picomoles; demonstrate identification or isolation of CTCs from clinical samples from cancer patients with sensitivity better than 10 cells per milliliter
  - o *In vivo* sensing platforms: Demonstrate identification of candidate biomarkers in bodily fluid samples (e.g., blood, urine, saliva, semen, etc.) containing artificially elevated concentrations of candidate biomarkers in appropriate animal models
  - o High throughput screening assays: Validate device using primary cells and/or tissues obtained directly from cancer patients
- Systematic study of sensitivity and specificity of the sensor platform in clinical samples – demonstrate reproducibility
- Collect data from a statistically significant number of patients in preparation for an IDE application
- Submitted IDE application to obtain necessary regulatory approval for clinical validation

302 Development of Clinical Automated Multiplex Affinity Capture Technology for Detecting Low Abundance Cancer-related Proteins/Peptides

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Quantitative detection of disease-specific proteins in serum and other bodily fluids forms the basis of many diagnostic tests to direct therapy in diverse areas of clinical medicine. Current methods for protein detection, however, are limited by their sensitivity or multiplexing capacity. Multiplexing capability is becoming a critical parameter in clinical biomarker evaluation, as testing practices employing a single marker do not have the performance characteristics required to enable critical decision making. While some new technologies capable of measuring multiple biomarkers in a single assay have emerged, they still suffer from low precision, low specificity, and automation challenges, as well as an inability to detect physiological levels of low abundant proteins. Despite these shortcomings, the advantage gained by miniaturization, high sensitivity, high-throughput, and automation makes affinity/protein capture technologies potentially powerful for the quantitative detection of known protein markers and the discovery of new markers.

Therefore, the NCI is interested in proposals that focus on developing a quantitative automated high-throughput multiplex affinity/protein capture technology to detect low abundance cancer related proteins/peptides from bodily fluids (examples of "bodily fluids" include plasma or serum, urine, serous fluids collected from body cavities, saliva, and ductal lavage, but not cell lysates or tissue culture media). Proposals should describe how the proposed technology will be highly specific, highly selective and have ultra-sensitive detection capabilities (at least within the ng/mL range) with limited sample preparation. Proposals should also distinguish any new methods of multiplex fabrication, novel affinity/protein capture systems, and/or new detection/quantification systems. All responses must deliver a reasonable method for working with complex bodily fluids. In addition, maximum level of multiplexing, volume of sample requirement, and sample processing/analysis time must be addressed.

Project Goals (short & long term):

It is believed that cancer-related biomarker candidates will be in relatively low abundance in human bodily fluids. The development of effective technologies to accurately measure these proteins and improve our diagnostic capabilities by discerning diseased from non-diseased states requires the development of next-generation multiplex affinity capture technologies. The purpose of this project is to stimulate the development of automated multiplexed affinity capture technologies for the detection of low abundance cancer related proteins/peptides from bodily fluids in support of the Clinical Proteomic Technologies Initiative (http://proteomics.cancer.gov). In addition, this tool is to be applicable in Cancer Centers and other settings where NCI Investigators conduct clinical care.

Phase I Activities and Expected Deliverables:

- Demonstration of feasibility of the innovative approach.
- Produce an initial product prototype by working with the Clinical Proteomic Technologies for cancer (CPTC) community.
- Conduct product prototype usability testing with representative users (e.g. CPTC).
- Make modifications to the prototype based on results obtained from usability testing.
- Compare findings to ELISA-based technologies. Detection limits should aim to be measured and reported as absolute quantitations that surpass current ELISA measurements.
- Prototype requirements include sample volumes less than 50 microliters, multiplex a minimum of 5 markers, high sensitivity (detection limit lower than 5 picogram/microliter), high reproducibility (CV's less than 10%), and a broad dynamic range (gram/liter to nanogram/liter)
- Establish prototype revisions/additions to be implemented and tested in Phase II.
- Present findings to NCI's CPTC Evaluation Panel.
- Research should be proposed with quantitative feasibility milestones.

Phase II Activities and Expected Deliverables:

- Implement strategy and project plan for a fully functional quantitative, automated high-throughput multiplex affinity/protein capture technology for detecting low abundant cancer related proteins/peptides from bodily fluids.
- Specificity greater than 95%.
- Development of an affinity/protein capture technology with multiplexing capability up to 50 analytes (proteins/peptides) that implements the features, functions, and requirements developed in Phase I.
- Project to be done in coordination with the CPTC community to integrate the platform into the technology assessment programs and into the greater scientific community.

- Validate findings as compared to ELISA.
- Research should be proposed with quantitative feasibility milestones.

303 Development of Quantitative Multiple Reaction Monitoring Mass Spectrometry Assays for the Detection of Cancer Related Aberrant Proteins/Peptides

(Fast-track proposals will be accepted.)

Number of Anticipated Awards: 4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

The application of proteomics tools in the clinical setting lags far behind their use in basic science and drug discovery. Techniques such as ELISA, 2D gels, and mass spectrometry have been used for protein/peptide biomarker candidate's measurement, but these methods still suffer from an inability to quantitatively evaluate multiple markers in a single reaction and have not been optimized to monitor amplified, isoforms or mutated proteins. However, recent applications of mass spectrometry in clinical laboratories has brought a renewed interest to mass spectrometric assays as a more specific method capable of selectively targeting and studying protein biomarkers. In Multiple Reaction Monitoring Mass Spectrometry (MRM-MS) assays, peptides from proteins are detected via mass spectrometric analysis. The mass spectrometric aspect of these assays enables single-step detection of amplified proteins, isoforms, or mutated proteins and their individual quantification. Recent applications of MRM-MS technologies coupled with affinity enrichment and stable isotope dilution in research and clinical laboratories, have demonstrated the capability of these assays to selectively quantify protein biomarkers in tissue, plasma, and serum.

As a result, the NCI is interested in proposals that focus on developing multiplexed MRM-MS assays for the detection of amplified proteins, isoforms, or mutated cancer related proteins/peptides from human tissue or bodily fluids (examples of "bodily fluids" include plasma or serum, urine, serous fluids collected from body cavities, saliva, and ductal lavage, but not cell lysates or tissue culture media). Proposals should describe how the proposed technology will be highly specific, highly selective and will have high sensitivity with a detection limit lower than 1 nanogram/microliter with limited sample preparation. Proposals should also distinguish any new methods of multiplex fabrication, and/or new detection/quantification systems. All responses must deliver a reasonable method for working with complex bodily fluids. In addition, the maximum level of multiplexing, the volume of sample requirement, and the sample processing and analysis time, must be addressed. Surface enhanced laser desorption ionization (SELDI) MS will not be considered for this SBIR.

Project Goals (short & long term):

It is believed that cancer-related amplified proteins, isoforms, or expressed mutations may serve as biomarker candidates. The development of effective technologies to detect and accurately measure these proteins and improve our diagnostic capabilities by discerning diseased from non-diseased states requires the development of next-generation proteomic technologies. The purpose of this project is to stimulate the development of multiplexed MRM-MS assays for the detection of cancer-related amplified proteins, isoforms. or mutated cancer related proteins/peptides from human bodily fluids including plasma, serum, proximal fluids, or tissue in support of the Clinical Proteomic Technologies for Cancer (http://proteomics.cancer.gov). These MRM-MS assays may incorporate immunoaffinity techniques for the enrichment of the protein/peptide targets before MRM-MS analysis. The MRM-MS assays may be protein or peptide based. Therefore, applicants may develop MRM-MS assays for the detection and quantification of cancer-relevant intact aberrant proteins as well as MRM-MS assays targeting peptides derived from the proteolytic digestion of such proteins. In addition, this tool is to be applicable in Cancer Centers and other settings where NCI Investigators conduct clinical care.

Phase I Activities and Expected Deliverables:

- Demonstration of feasibility of the innovative approach.
- Produce an initial product prototype by working with the Clinical Proteomic Technologies for cancer (CPTC) community.
- Conduct usability testing with product prototype with representative users (e.g. CPTC).
- Make modifications to the prototype based on results obtained from usability testing.
- Prototype requirements include sample volumes less than 50 microliters (for biofluids) or less than 2 mg wet weight for tissue, multiplex a minimum of 5 markers, high sensitivity (detection limit lower than 1 nanogram/microliter), high reproducibility (CV's less than 15%), and broad dynamic range (gram/liter to nanogram/liter)
- Establish prototype revisions/additions to be implemented and tested in Phase II.
- Present findings to NCI's CPTC Evaluation Panel.
- Research should be proposed with quantitative feasibility milestones.

Phase II Activities and Expected Deliverables:

- Implement strategy and project plan for a fully functional quantitative, high-throughput multiplex MRM-MS technology to detect aberrant proteins.
- Specificity greater than 95%.
- Development of an MRM-MS technology with multiplexing capability of up to 50 analytes (proteins/peptides) that implements the features, functions, and requirements developed in Phase I.
- Project to be done in coordination with the Clinical Proteomic Technologies Initiative community for integration into technology assessment programs and the greater scientific community.
- Research should be proposed with quantitative feasibility milestones.

304 Development of Blood-based Methods for the Detection of Cancer Recurrence in Post-Therapy Breast Cancer Patients

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $300,000 for 9 months; Phase II: $2,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Following skin cancer, breast cancer is the most common form of cancer in women, with an incidence of 13%. An estimated 192,000 new cases of invasive, and 62,000 cases of in situ (non invasive) breast cancer are expected to be diagnosed in 2010. Moreover, breast cancer is the number one cause of cancer death in Hispanic women and the second most common cause of cancer death in white, black, Asian/Pacific Islander, and American Indian/Alaska Native women. Over 40,000 women are expected to die of breast cancer in 2010.

Most women with breast cancer undergo surgery to remove the cancerous tissue and then receive additional treatment (adjuvant therapy), such as chemotherapy, hormone therapy, targeted therapy, or radiation. Adjuvant therapy does not completely remove the risk of late cancer recurrence, even for women with low grade/low stage tumors. Thus, clinicians and patients still need to remain aware of this problem and this problem remains a high priority in our fight against breast cancer.

A 2008 study of the risk of recurrence in 3000 women with stage I, II, and III breast cancer suggests that approximately 20% of breast cancer survivors who have completed 5 years of adjuvant therapy suffer a recurrence within 10 years after their treatment. Overall, the rates of recurrence were at 11% after 5 years and 20% after ten years following the completion of adjuvant therapy. The chances of recurrence increased with stage and the 5-year post adjuvant therapy rates were 7%, 11%, and 13% for women with stage I, II, and III, respectively.

Breast cancer can recur at any time, but most recurrences occur in the first three to five years after initial treatment. Breast cancer can come back as a local recurrence (in the treated breast or near the mastectomy scar) or as a distant recurrence elsewhere in the body. The most common sites of recurrence include the lymph nodes, bones, liver, or lungs.

Currently the only way for women who have been treated for breast cancer to check for recurrence is through self breast self-examination, checking both the treated area as well as the other breast each month.

Project Goals:

The aim of this project is to stimulate the development of novel blood-based assays for the detection of breast cancer recurrence indicators, including cytokines and circulating tumor cells. The applicants are expected to have access to a sufficient number of patient blood samples that would enable them to achieve the statistical power needed to prove the sensitivity and specificity of the assay for predicting cancer recurrence. If working with proteins, the applicants are expected to have already identified the proteins of choice and to be poised to test these in blood samples from both cancer-recurrence positive and negative patients.

Phase I activities and expected deliverables:

- Test predictive ability of the proposed assay on a statistically significant number of samples (e.g. 100) from post-therapy cancer patients who are cancer free 5 years past adjuvant therapy and a statistically significant number of samples from cancer patients who had disease recurrence 5 years past adjuvant therapy.

Phase II activities and expected deliverables:

- Test predictive ability of the proposed assay on a statistically significant number of samples (e.g. 500) from post-therapy cancer patients who are cancer free 5 years past adjuvant therapy and a statistically significant number of samples from cancer patients who had disease recurrence 5 years past adjuvant therapy.

305 Novel Digital X-ray Sources for Cancer Imaging Applications

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: $250,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Medical imaging is extensively used in clinical management of cancer patients. Key medical imaging modalities such as Computed Tomography (CT), digital radiography, fluoroscopy, and mammography use X-rays and play an important role in cancer screening, diagnosis, and treatment. At the present time, however, all clinical imaging systems produce X-rays using vacuum tubes that have high cost, high weight, and relatively low reliability. Conventional design of vacuum tubes puts constraints on the geometries of medical imaging systems, and leads to decreased reliability and increased cost. Novel approaches to the manufacturing of multi-pixel digital X-ray sources are emerging that are enabled by developments in nanotechnology, material science, and micro-fabrication. These approaches, if successful, will lead to a new generation of cancer imaging devices.

The purpose of this contract topic is to stimulate the construction and commercialization of innovative multi-pixel X-ray sources to be incorporated in clinical modalities, including: digital breast tomosynthesis, fluoroscopy, computed tomography, and digital radiography. It is expected that the proposal will specify clinical applications of the proposed X-ray source technology.

The Phase I proposal MUST address the following:

1) What are the desired performance parameters of the proposed X-ray source required for a specific cancer imaging application (kVp, resolution, energy spectrum, output, etc.)? Which performance parameters are achievable?
2) What temperature stability is required for the application?
3) What thermal management system will be required for the X-ray source, and will it be feasible to build one?
4) A detailed estimate of the expected cost of manufacturing the X-ray source once it has been developed.
5) An assessment of the Intellectual Property landscape, including an analysis of freedom to operate, and of the patentability of the proposed source design.

Project goals:

The short-term goal of this project is to develop a prototype of the innovative multi-pixel X-ray source with performance characteristics suitable for cancer imaging. The long-term goal of this project is to develop medical imaging system designs incorporating innovative X-ray radiation sources. These system designs should significantly reduce the cost of imaging systems, make them more portable, enable new image-guided procedures, and positively impact clinical outcomes.

Phase I Activities And Expected Deliverables:

Phase I activities should support the technical feasibility of the proposed innovative approach. Specific activities and deliverables during Phase I may include:

- Design and build proof of principle prototype of the X-ray source and collimator system
- Characterize the X-ray source (spectrum, flux, spatial resolution, point spread function, etc)
- Assess the stability of the source
- Design a concept for a thermal management system adequate for the prototype system

Documentation providing a top-level description of the prototype system design, validation protocol, and testing results should be provided to NCI as part of the Phase I final report.

Phase II Activities And Expected Deliverables:

Phase II activities should support further development of the X-ray source as well as design of the prototype imaging system employing the source.

- Design and produce a full-scale X-ray source prototype supporting a specific clinical application

- Design and produce a prototype thermal management system
- Characterization of source performance parameters
- Design and build a prototype imaging system incorporating the developed X-ray source
- Perform measurements of performance parameters for the developed imaging system such as uniformity, spatial resolution, contrast, etc.

306 Development of Innovative Algorithms/Software for Processing & Analysis of In Vivo Images in Oncology

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 2-4

Budget (total costs): Phase I: $200,000 for 9 months; Phase II: $1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Image processing algorithms are increasingly important as imaging and image-guided intervention technologies become critical in screening, diagnosis, staging, treatment, and monitoring of cancer patients. The use of *in vivo* imaging modalities such as MRI, X-ray, CT, Positron Emission Tomography, Nuclear Medicine, Ultrasound, Optical Coherence Tomography, and Photo-acoustic imaging, as well as multi-modality imaging for the management of cancer patients, has continued to increase exponentially. As more and more imaging data becomes available, innovative image processing and analysis software algorithms are essential to effectively exploit the information presented by medical images.

Improved image processing and analysis software is critical to serving the needs of cancer patients by enhancing the ability to distinguish viable cancer from necrotic cells, swelling, or other benign causes of persistent radiographic abnormalities. Advanced software also allows the radiologist to detect cancer earlier, when treatments may be more effective and to perform a non-invasive or image-guided needle biopsy approach to diagnose cancer and avoid an open surgical procedure. In many cases, advanced visualization and post processing algorithms enable faster and more accurate assessment of disease extent to guide treatment options, both at the time of diagnosis and during treatment.

Project goals:

The short-term goal of this topic is to develop robust algorithms to enable faster and more accurate decision making for imaging and image-guided interventions. These include the following:

- Algorithms that enable real-time reconstruction and display of images for image-guided interventions
- Extraction of clinically relevant quantitative information from images.
- Improvements in multimodality image co-registration, image fusion and deformable models for image visualization, and image-guided interventions.
- Optimization in image processing techniques that enhance visualization (e.g. segmentation tools, noise reduction, etc.) and facilitates image analysis.
- Novel methods for feature extraction and object recognition to develop tools for computer-aided detection (CAD) and monitor changes over time.

- Algorithms to quickly process large image data sets.

Projects developing algorithms for image acquisition and/or routine image processing for a new medical imaging device should not be submitted. Image processing algorithms that are vendor independent and can be applied to multiple modalities are strongly encouraged by the NCI. However, this does not exclude the possibility that commercialization may be executed initially through a single vendor.

It is expected that the proposed innovation will be driven by clinical practice. Therefore, in addition to standard proposal components, the contract proposal must contain specific discussion of the target patient population and evidence of an existing clinical problem which is addressed by the proposed method. The proposal must also contain an analysis of competitive methods to address the same problem and explanation of competitive technical advantages of proposed algorithm. All Phase II proposals MUST contain a section entitled “Regulatory Plan” that demonstrates an understanding of the regulatory requirements for clearing the software device through the FDA, details the company’s plan to meet the requirements, and explains how the proposed work helps to meet these requirements. If regulatory approval is not expected to be required, the offeror must provide an extensive justification for this.

The long-term goal of the program is to create software packages with novel algorithms that can be integrated into one or more different commercial imaging platforms, where appropriate.

Applicants are encouraged to explore affiliations with the NCI Research Networks such as the Quantitative Imaging Network (QIN) (http://grants.nih.gov/grants/guide/pa-files/PAR-08-225.html), which aims to develop a consensus on methods to validate software and modeling methods, share ideas and approaches to validate and standardize imaging data, and explore related imaging metadata for quantitative measurements of responses to cancer therapies.

Phase I Activities And Expected Deliverables:

- Development of an innovative algorithm to improve image processing methods for imaging or image-guided interventions for cancer patients.
- Preliminary validation of the algorithms in phantoms or clinical patient image data-sets, as appropriate. The NCI Cancer Imaging Program has a link to publically available resources for digital image data-sets: (http://imaging.cancer.gov/programsandresources/InformationSystems/ImageArchiveResources/page14)
- In-person software demonstration to NCI Program staff (travel to NCI must be included in the budget)
- Final progress report should include plans for distribution of the product as part of the commercialization objectives. If cooperation of other companies or large equipment manufacturers is required for commercialization, the report should provide evidence of established communication with potential partners.

Phase II Activities and Expected Deliverables:

- Establishment of an FDA-compliant Quality System for software development
- Production of a clinic ready software package with user-friendly graphical user interface
- Extensive clinical validation using reader studies with prospective data to demonstrate improvements from the developed algorithms including usability as compared to current standard of care
- Draft user manual
- Provide Standard Operating Procedure for clinic-ready software to NCI
- Present final results to NCI

307 Novel Imaging Agents to Expand the Clinical Toolkit for Cancer Diagnosis, Staging, and Treatment

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I offerors with their long-term strategic planning.)

Number of Anticipated Awards: 3-5

Budget (total costs): Phase I: $250,000 for 9 months; Phase II: $1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

Medical imaging plays a key role in clinical management of cancer patients. Cancer imaging agents are used in conjunction with medical imaging equipment, and, by highlighting the contrast between normal and malignant tissues, they allow the collection of information on cancer presence, spread, and metabolism.

Recent scientific advances in nanotechnology, radiochemistry, reporter gene imaging, and other fields now enable the development of novel imaging agents for:

- Early detection and diagnosis of cancer
- Differentiation of benign disease from malignancy
- Stratification of patients for the purpose of selecting a cancer therapy
- Surgical planning
- Evaluation of tumor response to chemotherapy and radiation therapy
- Detection of cancer recurrence

However, despite significant preclinical scientific progress, very few cancer imaging agents are actually available in the clinic. Therefore, this SBIR contract topic seeks to stimulate the commercialization of novel imaging agents, including: nanotechnology-based imaging agents, radiopharmaceuticals for positron emission tomography (PET) and single photon emission computed tomography (SPECT), targeted contrast agents for X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), optical contrast agents, reporter gene imaging technologies.

Project goals:

The short-term goal of this SBIR contract topic is to support research and development activity at small businesses that are developing cancer imaging agents. The work scope may include animal testing, formulation, GMP production, pharmacokinetic, pharmacodynamic, and toxicological studies. These data will support the rationale for continued development of the experimental medical imaging agent to the point of filing an Investigational New Drug application (IND).

The long-term goal of this contract topic is to enable small businesses to bring novel classes of fully developed cancer imaging agents to the clinic and the market. Therefore, businesses are encouraged to submit applications for development of lead compounds representing novel technology platforms.

Phase I Activities And Expected Deliverables:

Phase I activities should generate scientific data confirming the clinical potential of the proposed contrast agent. Some of the expected activities are:

- Preparation of an imaging agent

- Proof of concept pre-clinical studies
- Preliminary toxicological studies
- Preparation of a development plan that describes in detail the experiments necessary to file an IND or an exploratory IND
- Presentation of the Phase I results and the development plan to NCI staff

The Phase I research plan must contain specific, quantifiable, and testable feasibility milestones.

Phase II Activities And Expected Deliverables:

Phase II should follow the development plan laid out in the Phase I, and should further support commercialization of proposed cancer imaging agents. Some of the expected activities are:

- Completion of all pre-clinical experiments according to the development plan
- Production of sufficient amount of clinical grade material suitable for an early clinical trial
- If warranted, filing of an IND or an exploratory IND for the candidate imaging agent
- Completion of a small-scale clinical study

Phase II research plan must contain specific, quantifiable, and testable feasibility milestones.

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE (NCCAM)

The National Center for Complementary and Alternative Medicine (NCCAM) is the Federal Government's lead agency for scientific research on the diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. NCCAM sponsors and conducts research using scientific methods and advanced technologies to study CAM.

This solicitation invites proposals in the following areas.

001 Develop Analytical Methodologies to Validate Label Claims for the Most Commonly Used Botanicals and Dietary Supplements

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Number of Anticipated Awards: 1-2

Dietary supplements are used by a large portion of the U.S. population. However, numerous reports have indicated that the product composition is not always consistent with the claims made on the label. Examples include insufficient amounts of the described herb, substitution with different species, and inconsistent concentrations of marker compounds. Furthermore, contamination either with pharmaceutical substances or other toxic chemicals has been reported.

Research into dietary supplements is compromised when there is uncertainty regarding the products being used in these studies. In order to make progress in understanding the biological effects of dietary supplements it is imperative that there be confidence regarding the identity and characterization of substances being investigated.

The purpose of this SBIR contract topic is to encourage laboratories with appropriate expertise and facilities to analyze the most common dietary supplements and compare their compositions with what is declared on the product label, certificate of analysis, or other documentation. The methodology may include commonly used techniques such as HPLC and MS, but investigators are encouraged to incorporate more novel methods which are not chromatography based.

Phase I research is expected to focus on development and validation of appropriate methods. These will include determining the identity of the specified herb, the presence of any contaminants (e.g. adulteration with different species, pharmaceuticals, heavy metals, pesticides, etc.), and concentration of selected marker compounds.

Phase II should include implementation of methods developed in Phase I and testing of a wide variety of commercially available samples.

002 Comprehensive Biological and Phytochemical Analysis of *Harpagophytum procumbens* (Devil's Claw)

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Number of Anticipated Awards: 1-2

Harpagophytum procumbens, or Devil's Claw, is a plant native to the southern part of the African continent. It has been studied as a treatment for osteoarthritis, rheumatism, and low back pain. A number of possible mechanisms for the observed clinical effects have been investigated including anti-inflammatory and antioxidant activity. The benefits of this herb are most often attributed to the iridoid glycosides present of which harpagoside is the most prominent. However, some of the biological effects associated with this plant are thought to be due to other constituents. For example, the crude extract of the plant has been shown to have anti-inflammatory activity, but there was comparable activity with a harpagoside-free extract. Numerous other compounds have been identified from this plant including various sugars, triterpenes, flavonoids, and other phenolics. It is possible that these components, or other undiscovered minor metabolites, may make significant contributions to the overall activity of this medicinal plant.

The purpose of this SBIR contract topic is to conduct a thorough biological and phytochemical analysis of *Harpagophytum procumbens*. This should result in discovery of new biologically active molecules and/or a more comprehensive understanding of the contributions made by the known constituents. It is expected that a bioactivity-based fractionation approach would be followed to identify compounds which act through the various hypothesized mechanisms. Identification and structure elucidation of novel compounds is encouraged.

Phase I would be expected to include identification of a source for the plant material and set up of the various assays. Development of an extraction method and establishing an analytical method for the characterization of the extract and subsequent fractions would also be appropriate.

Phase II should include determination of fractionation protocols adequate to separate the various classes of compounds. The fractionation should be directed by the activity of interest. This stage of research should include a plan for the rapid identification of known compounds from the plant based on comparison of chromatographic, spectroscopic and spectrometric data with reference sources. Phase II should culminate in the creation of a database of compounds identified and their associated activities.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the tools and training they need to understand, detect, treat, and prevent a wide range of diseases. NCRR supports all aspects of clinical and translational research, connecting researchers, patients, and communities across the nation. This support enables discoveries made at a molecular and cellular level and through animal-based studies. These discoveries are translated to patient-oriented clinical research, with the ultimate aim of improved patient care. Through its programs, NCRR stimulates basic research to develop and provide access to state-of-the-art technologies and instruments for biomedical and clinical research; improves the public understanding of medical research; and provides information about healthy living. NCRR supports all aspects of clinical and translational research, connecting researchers, patients, and communities across the nation.

This solicitation invites proposals in the following areas.

012 Visualizing Biomedical Research Characteristics

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 2

The complexity of NCRR programs requires an innovative approach to both understanding scientific developments at large and managing its scientific portfolio. Biomedical research can be characterized in a multitude of ways. Publications, grant applications/proposals, progress reports, funding, specific aims, experimental designs, hypotheses, outcomes, scientific evidence, experts, collaborations, organizations, and networks, as well as many other factors reflect the complex activity of biomedical research. These elements are interlinked and often are represented by large volumes of data, e.g., thousands of papers are produced weekly. To make sense of these data and to aid in seeing the big picture, new methods are needed. Visualization has proven to be useful for extracting information from abundant data. A variety of scientific visualization techniques enable us to identify patterns and relationships and provide other useful information, especially for the process of making decisions. NCRR invites SBIR proposals that will facilitate the introduction of visualization technology into understanding the big picture of science, management of a research portfolio, and communication of complex scientific information.

Main requirements:

The outcome of this contract is expected to be software that assists in exploring multidimensional textual data, understanding complex concepts, and portfolio analysis. The software must

- visualize massive amounts of high-dimensional data from potentially diverse data sources according to the customers' values and requirements
- enable data exploration, change of displayed dimensions, and semantic zooming
- be able to work with complex data dimensions, utilizing the elements of principal component analysis (PCA) or other appropriate techniques
- have transparent, validated, and well-documented protocols for all steps of data processing (cleansing, filtering, analysis, visualization, personalization, etc.)
- be accompanied by documentation of data processing algorithms, data accuracy, precision, and other features necessary for the most accurate interpretation of the produced visualization
- have Application Programming Interface (API) that does not require programming skills

Sample areas of interest to NCRR

Current state of knowledge, science, and funding

- Landscape of knowledge that enables exploration of underlying evidence
- Visual thesaurus of complex scientific concepts
- Map of existing standards and their applicability and usefulness for specific tasks and environments, which may assist in choosing one or a combination for a project
- Visualizations that assist in navigation of complex and distributed on-going research activities
- Map of NCRR-related entities, expertise, activities, collaborative projects, funding, networks; e.g., Clinical and Translational Science Awards (CTSA) displaying multiple layers of communities and collaborative research activities

- Distribution of funding among various scientific domains, institutions, types of grantees, and mechanisms
- Network model of science where locations and interconnectivity of entities (e.g., scientists, organizations, papers, or concepts) can be explored

Evolution of science and pathways to success

- Evolution of scientific domains, experts, collaborations, and concepts
- Pathways for translating discovery into innovation
- Productive career pathways, e.g., those leading to significant achievements
- Success factors for translational research, e.g., infrastructure, people, funding
- Scientific forecasts

Health

- Landscape of knowledge about human health
- Pathways to health, e.g., how people find and utilize health information
- Visualizing differences in understanding of health in various cultures and communities

Deliverables

The deliverable of Phase I is a visualization of a test dataset(s), which is made meaningful and valuable to NCRR through the process of interactive learning with minimal burden on the experts. It is envisioned that the contractor's representative will gather initial information from publically available sources, and then fine-tune it via observing NCRR meetings, capturing the discussion points relevant to the topic of the project in a way that engages the audience and enables its immediate feedback, and asking targeted questions. The techniques may include both computerized and manual approaches such as whiteboard and sticky notes. This process will ensure that the presentation of data and analysis is tailored to NCRR interests and facilitates actions, discussions, feedback, and further learning.

The Phase II deliverable is web-enabled software that can be used for multidimensional data exploration and portfolio analysis, can work with multiple data sources, and can be personalized to the customer needs via generalized interactive learning methodology of Phase I.

Data and information use agreements may need to be signed.

Visualization implementation

Various visualization techniques can be used. Examples of visualizations can be found at http://www.scimaps.org and include knowledge/domain/concept maps, networks, and innovative ways to display complex concepts.

Data sources

The analysis should be done using a number of various data sources, e.g., publications, World Wide Web, and NIH databases. The identification of appropriate sources is determined by the offeror. The choices must be justified, analyzed, and well documented with advantages and limitations of every source.

Other project clarifications

The offerors are encouraged to utilize the multiple principal investigator option to bring in experts from academia http://grants.nih.gov/grants/multi_pi/.

014 Equipment, Supplies and Chemical Solutions Required for High-throughput Cryopreservation of Sperm from Biomedical Model Fishes

(Fast-Track proposals will be accepted.)

Number of Anticipated Awards: 2

Summary

The ability to produce transgenic, knockout, and mutant stocks of a variety of fish species has provided biomedical researchers with many useful animal models for the study of human diseases. However, the requirements to maintain live animals can overwhelm the capacity of even the largest stock centers. Although cryopreservation of gametes is a proven method for long-term maintenance of genetic material in some animals, in others it is still suboptimal and cannot be extrapolated to other strains or species. As aquarium fishes (zebrafish, medaka and *Xiphophorus)* are becoming increasingly important because of their value in biomedical research, few studies have addressed sperm cryopreservation in these models. Most notable of those species studied is the zebrafish for which sperm cryopreservation techniques, standardized protocols, scaling-up for commercial production, inventory procedures and quality control are being addressed. As there are many ongoing and planned large scale mutant, gene knockout and screening projects, there is a need for the development of "high-throughput" and scalable technologies to address the preservation of these large numbers of genetically engineered fish. "High-throughput" or the capability for large-scale processing, involving automated systems, is the greatest current need for aquarium fish cryopreservation.

This contract topic seeks to stimulate research and development of cryopreservation capabilities (equipment, supplies and chemical solutions) that will be available commercially as a standardized, streamlined process, involving 2 or 3 pieces of equipment, requiring minimal laboratory space and that could be maintained and operated efficiently by a single person. Ideally, most of the process would be automated and all of the components listed below (equipment, supplies and chemical solutions) should be integrated into a single unified platform, similar to that developed for processing of mammalian sperm. Short of complete integration of all aspects, priority will be given to integration for each of two sub-groupings: 1) a single microfluidic platform for sperm collection, processing, and quality assessment, and 2) an approach for packaging and freezing of samples that should likely involve two pieces of equipment (packaging and freezer). The containers (such as straws) should be matched to the packaging system and storage methods. Chemical solutions should be of high quality and be pre-packaged for use. It is anticipated that successful offerors will currently have a similar platform in place for mammalian species and can present plans for efficiently adapting to aquarium fishes.

1. Equipment Needed for Specific Activities

Collection, processing, and quality assessment of samples

- Device for sperm collection from live males
- Microfluidic devices (preferably integrated):
  - Estimation of sperm concentration
  - Dilution of samples to specified concentration
  - Controlled pooling of samples
- Microfluidic devices suitable for sperm quality analysis including:
  - Motility (e.g., computer-assisted sperm analysis)
  - Cellular characteristics (e.g., morphology, membrane and mitochondrial integrity)

Packaging and freezing of samples

- Integrated automated instrument capable of handling 10-100 µl volumes for:
  - Filling of containers

- Alphanumeric labeling of containers
- High-biosecurity sealing of containers
- Label verification

- Bench-top sized, electric device for freezing without liquid nitrogen

Storage and Inventory of frozen samples

- Method for sorting and packing of frozen samples prior to storage in liquid nitrogen

2. Supplies Needed for Specific Activities

- Containers (e.g., straws) suitable for 10-100 µl volumes with no sample loss
- Multi-compartment racking systems for storage of frozen samples
- Software for tracking of inventory and linkage to databases

3. Chemical Solutions Needed for Specific Activities

- Prepackaged, high quality, sterile solutions, tablets, or powder mixes for:
  - Extender solutions for sperm collection, dilution, and refrigerated storage
  - Extender with cryoprotectant (methanol)
  - Fertilization solution
- Reagent kits for standardized sperm quality analysis

Project goals:

The short-term goal of the project is to perform proof-of-principle technical feasibility demonstration of "high-throughput" cryopreservation technologies for aquarium fish sperm collection, evaluation, processing and storage. The long-term goal of the project is the development of cryopreservation capabilities (equipment, supplies and chemical solutions) for large-scale processing of fish sperm that will be available commercially as a standardized, streamlined process.

Phase I activities and expected deliverables:

Phase I activities should support the technical feasibility of the approach. Specific activities and deliverables during Phase I should include:

- Design of a prototype system(s)
- Validation of the prototype system(s)
- Documentation providing a top-level description of the prototype system design(s), validation protocol(s), and testing results should be provided to NCRR as part of Phase I progress report.

Phase II activities and expected deliverables:

Phase II studies should further refine the technology or strategy and test its effectiveness for incorporation into the research setting.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigation, and trials, observational studies, and demonstration and education projects. The Institute's mission includes studies related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung,

blood, sleep disorders, and blood resources management. Studies are conducted in its own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The NHLBI SBIR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

This solicitation invites proposals in the following areas.

043 Development of Pathogen Inactivation Technologies for Blood Components

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-3

Great strides have been made over the past 25 years vastly improving the safety of the nation's blood supply. Current blood donor screening and laboratory testing has drastically reduced the risks of acquiring infectious disease through blood transfusion. However, the potential for new, emerging infectious agents entering the blood supply continues to be a serious concern of the blood banking community. Pathogen inactivation of blood and blood components provides an additional layer of protection from such agents. The effectiveness of pathogen inactivation technology is best exemplified with the virtual elimination of certain infectious agents from manufactured plasma derivatives. Since 1985, there have been no transmissions of human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) by U.S. licensed plasma derivatives. However, because of the labile nature of red blood cells and platelets, these technologies are far too harsh for use with cellular blood components. During the past several years, new technologies have been developed and evaluated in clinical studies offering hope that blood components can also be treated to destroy the infectivity of a wide array of microbial agents without significantly reducing the components' therapeutic effectiveness. These technologies include leukoreduction of blood, photochemical treatment of platelets or plasma with ultraviolet light and psoralen compounds, and various chemical treatments of red blood cells which may or may not involve irradiation with ultraviolet or visible light. Some of these technologies have been shown to reduce infectivity in a wide array of infectious agents. While much progress has occurred in the development of these technologies in recent years, there is still no U.S. licensed pathogen inactivation process for cellular blood components. There is a need to evaluate other new, promising compounds and procedures. It does not appear that any one inactivation technology will be effective in treating all classes of agents (e.g., viruses, bacteria, protozoa, prions). It is likely that a combination of techniques that remove and/or inactivate agents will be needed. These technologies are generally sophisticated and costly. They probably will be utilized by the developed world if found to be safe and effective. However, because of costs they will be out of reach for resource-poor countries where blood-borne agents are highly prevalent and laboratory screening irregular or nonexistent. In such settings, the availability of simple, cost-effective inactivation procedures could save millions of lives. This contract topic encourages research leading to the development of pathogen inactivation procedures for blood components, particularly red blood cells and platelets. Work on plasma components would also be responsive to this solicitation. Research on the development of simple, low cost procedures for use by less practiced laboratory personnel in the developing world would also be responsive and is highly encouraged.

The Phase I proposal shall focus on studies that provide proof of concept that the pathogen inactivation procedure is capable of reducing the infectivity of infectious agents in the blood component(s) while maintaining the function of the component at an acceptable therapeutic level. The inactivation kinetics of the infectious agents being studied shall be determined. The effect of the procedure on the viability of the blood component shall be determined using a variety of different approaches depending on the component such as flow cytometry studies to determine the extent of platelet activation, platelet aggregation studies or assays for the red cell storage lesion (e.g., extracellular potassium leakage).

Phase II studies will extend the efforts of the Phase I studies and shall focus on in vitro and in vivo studies and scale-up of the process and prototype device including ancillary equipment such as blood bags. Studies shall include the use of human blood in quantities comparable to those amounts to be treated in the blood bank. In vivo studies shall be designed to demonstrate acceptable product performance as predetermined by FDA regulations (RBC) or by agreement with FDA staff (platelets). The array of infectious agents to be tested can be expanded in this phase. The therapeutic effectiveness of the component shall be investigated. Safety studies of the treated

component shall be conducted and shall include toxicity, reproductive toxicity, and mutagenic and carcinogenic potential.

057 Point-of-Care Assay for Engraftment Potential of Umbilical Cord Stem Cells

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-3

Hematopoietic (blood-forming) stem cells circulate in the blood of fetuses and are abundant in placental umbilical cord blood. Umbilical cord blood is normally discarded with the placenta after the baby is born. Since 1988, umbilical cord blood has advanced as an alternative source of stem cells for bone marrow transplantation and increased the pool of available donor stem cells with no risks to the donor. Umbilical cord stem cell transplants may cause less graft-versus-host disease and graft rejection in recipients because the naïve immune systems of newborns are more tolerant to host tissue than immune cells from older children and adults. The successful advances in umbilical cord blood transplantation are important for emerging fields of cellular therapies and regenerative medicine, including induced pluripotent stem cells.

Research on the collection and use of umbilical cord blood (UCB) for clinical use has been supported by the Transfusion Medicine and Cellular Therapeutics Branch, Division of Blood Diseases and Resources at the National Heart, Lung, and Blood Institute (NHLBI) in three major areas:

- Development of standard operating procedures for collecting, processing, storing and shipping UCB for stem transplantation,
- Determination of the efficacy of UCB as a potential stem cell source for patients with malignant and non-malignant blood diseases, and
- Improvement of the outcomes of UCB transplantation.

Hematopoietic stem cell transplantation can be lethal if the transplanted cells fail to grow in the recipients. Laboratories assess the quality of cord blood products by performing colony forming assay cultures, often requiring up to 14 days before results are known; or counting the total nucleated cells and quantifying CD34+ cells by flow cytometry before the cord blood products are frozen and banked. Standardization of in vitro colony forming assays is difficult and results are often discrepant between laboratories. There is a critical need for improved bioassays that are quantitative, reproducible, readily performed, and predict the engraftment potential of cord blood stem cells. The goal of this solicitation is to address this challenge by providing a funding opportunity for the development and production of new bioassays to rapidly determine the engraftment potential of cryopreserved UCB stem cells prior to transplantation. The bioassays must be validated using existing assays as comparators and applicants must develop a production plan to commercialize the assay.

Phase I proposals should focus on the development of a bioassay for research applications. Investigations in this phase will involve laboratory research.

Phase II proposals shall focus on scale-up and production of a bioassay for distribution. Assay validation will be required.

058 Novel Technologies for Powering Ventricular Assist Devices

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4-5

Because the heart transplant donor pool in the United States is less than 2,500/year, ventricular assist devices (VADs) are the only realistic option for many late-stage heart failure patients. Currently, each year 2,000-5,000 receive VADs to bridge them to a heart transplant or as permanent (i.e. “destination”) therapy. However, the VADs currently available rely upon batteries that, despite recent advances, require frequent recharging, weigh on the order of pounds, and must be carried by the patient. Furthermore, the percutaneous cables used to connect

the batteries and device controllers to the VADs provide a site for infection where the driveline crosses the skin. Consequently, the driveline site must be frequently cleaned to reduce the risk of infection.

Offerors will develop novel technologies for delivering power to VADs to successfully improve the quality of life and reduce the risk of infection associated with current methods for delivering power to VADs for chronic circulatory support. Examples of appropriate projects include (1) power and data transmission systems that do not require percutaneous drivelines and (2) innovative power sources which will reduce the size and weight of external batteries and the frequency of recharging them or, preferentially, eliminate external batteries altogether.

Phase I proposals should address initial development and feasibility testing of novel technologies for delivering power to VADs which can be applied to existing or new circulatory support devices. The technologies should have the potential to eliminate external batteries and/or percutaneous drivelines or make substantial improvements over existing power-related technologies for VADs so that the risk of infections is significantly reduced and the quality of life is improved. Preference will be given to proposals for technologies with the potential to eliminate external batteries and/or percutaneous drivelines.

Phase II proposals should be focused on completing the development of the technology such that it can be readily incorporated into circulatory support devices. The work is expected to include in vitro and in vivo studies to demonstrate effectiveness.

059 Informatics Tools and Services to Support Data Sharing and Distribution for Cardiovascular, Lung, and Blood Researchers

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

The NIH expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers. Investigators submitting an NIH proposal seeking $500,000 or more in direct costs in any single year (>$500K) are expected to include a plan for data sharing or state why data sharing is not possible. Detailed guidance on how awards of $500K or greater should share research data is available at http://grants.nih.gov/grants/sharing_key_elements_data_sharing_plan.pdf. While some investigators are better situated and capable of complying with these goals, others are not as well prepared. The NIH recognizes that it takes time and money to prepare data for sharing, so to meet the goals of the program, investigators may request funds for data archiving and sharing as part of the proposal (http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm#a22).

This SBIR contract topic would support small businesses to develop tools and services that assist investigators in developing and implementing the data sharing plans across the cardiovascular, lung, and blood research fields. Approaches could vary from hosting the data on their own servers or through cloud computing to those who format the data using standardized formats and annotations then submit them to existing repositories. Proposals may focus on assisting researchers in specific fields to utilize existing data resources through developing and deploying software tools and services that make implementing data sharing more accessible. Alternatively, proposals may provide tools and services to support data annotation and hosting services for a broad array of biomedical sciences across heart, lung and blood research that do not yet have existing data warehouses or repositories. Informatics tools and services provided under this program should include:

- Data sharing plan descriptions and budgets that comply with the Key Elements guidance that investigators may include in grant applications.
- Tools, resources, and services to implement the data sharing plans. These include annotation of datasets using standardized ontologies, terminologies, or controlled vocabularies; compliance with accepted data format, data transfer, and metadata representation procedures; and ensuring data is properly uploaded into the data repositories specified in the data sharing plan.

Proposals should use existing resources for data sharing or annotation where possible. Thus, proposals should identify which existing data repositories, controlled vocabularies, terminologies, ontologies, and metadata

standards they will be using. Proposals should clearly indicate which data sharing and annotation best practices they are re-using to facilitate data sharing and should also highlight the new informatics tools and services they will be developing and providing to researchers to support their data sharing plans.

The Phase I proposals should focus on developing prototypical data sharing plans that describe data annotation and sharing services provided by their small business. Phase I proposals should also implement annotation and data upload of test suites of data. The proposal should identify the target population of the Phase I test case. The proposal should outline the outreach and marketing strategy for disseminating information about their tools and services to the targeted research community.

The Phase II proposals should focus on scale up and production of the informatics tools and services to a broader array of cardiovascular, lung, and blood researchers. Validation of annotation and upload of data sets will be required, as will tests to find and download data sets from the data repositories. The proposal should identify and assess outreach and marketing strategies and should provide a plan for ensuring adoption of community best practices for data annotation and/or sharing during the duration of the award.

060 Interventional MRI and X-ray Invasive Hemodynamics Telemetry

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Background

Magnetic resonance imaging (MRI) has potential to revolutionize minimally invasive surgery and interventional procedures, by affording improved tissue visualization without conventional surgical incisions. Many such procedures will be conducted under both X-ray and MRI guidance.

Invasive and interventional cardiovascular procedures require high fidelity hemodynamic recording for diagnostic measurement as well as procedural monitoring of physiological signals such as electrocardiography and invasive blood pressure.

There are no commercially available invasive hemodynamic recording systems available for MRI, or for dual MRI and X-ray use. MRI creates specific challenges for the recording and transmission of physiological signals. (1) Multiple sources of noise in the MR environment distort physiological signals, including radiofrequency pulses, rapidly switching magnetic field gradients, and induced voltages from the flow of blood in a static magnetic field (magnetohydrodynamic effect). (2) Transmission lines for physiological transducers are susceptible to heating during radiofrequency excitation. (3) Connections between the patient transducers or electrocardiography leads and the recording system must be interrupted for intermodality transfer between the X-ray and MRI interventional systems, and this interruption may be required during critical periods of clinical instability. (4) Commercially available leads, transmission lines, and transducers may not have features required both for X-ray (for example, radiolucency) and for MRI (for example, avoiding loop formation, attenuating heating, etc). (5) Physiological signals acquired in the MR environment will require preprocessing before transmission into conventional hemodynamic recording systems.

A high fidelity hemodynamic recording system is necessary to conduct interventional cardiovascular and other high risk procedures under MRI guidance and with seamless bidirectional transfer to and from X-ray. To date there are no suitable commercial solutions.

A wireless telemetry and preprocessing system is technically feasible that supports high fidelity hemodynamic recordings in a multimodality interventional environment using MRI and interventional X-ray. Such a system would allow acquisition of hemodynamic signals (multichannel electrocardiography, invasive blood pressure, hemoglobin saturation, temperature, etc) safely in either an MR environment or an X-ray fluoroscopy environment, preprocessing to remove identifiable noise, wireless transmission to base stations in both environments, and automated transmission of signal that conform automatically to inputs of a commercial hemodynamic recording system.

Specifications

Specifically, (1) the system must operate safely at MRI field strengths of 1.0 to 3.0T. (2) The system must record and transmit signals with the patient inside the magnet bore during imaging. (3) The system should have a signal preprocessing unit to filter MRI-specific noise. The system must handle noise caused by MRI radiofrequency pulses and gradient switching events and be robust to a range of rapid pulse sequences with continuous duty cycle, including single and multi-slice real-time, three-dimensional gradient echo, balanced steady state free precession, and (non-real-time) turbo spin echo techniques. The system must be able to filter noise from low frequency events, such as spoiler gradients or "preparation" sequences. The system may access the MRI gradient waveforms to filter or exclude noise related to low-frequency MRI gradient switching events. (4) The system should provide 9-10 electrodes for diagnostic electrograms (six standard ECG chest and 3-4 limb leads) under an X-ray environment and at least four electrodes for filtered surface electrograms (one chest, three limbs) under an MRI environment or for non-cardiac X-ray applications. Specific attention should be paid to robust and safe disposable electrode attachment to patient skin to address hair, perspiration, conductivity, and current flux density distribution for signal fidelity and risk of burns. The electrode and lead system should be safe for operation under MRI, resistant to inadvertent loop formation, and should be radiolucent for operation under X-ray even with extreme double-oblique projection angles. (5) The system should allow transduction of 2 simultaneous channels of invasive blood pressure from fluid-filled catheters, ideally with commonly used clinical invasive blood pressure transducers and continuous hemoglobin oxygen saturation. (6) All physiological signals should be aggregated in a single connector box (patient interface unit) for wireless telemetry. Signals must be received in at least one base station in each modality, (one in the X-ray lab and another in the MRI lab), with automatic or semi-automatic handoff from one to the other. Base stations should connect to popular commercial hemodynamic recording systems (specifically Siemens *Sensis* and General Electric *MacLab*). (7) Have a safe power source in patient interface unit that allows uninterrupted operation for at least 8 hours. (8) The system should NOT Interfere with MRI, i.e. the system should not generate radiofrequency noise that interferes with MRI of hydrogen, carbon, fluorine, and phosphorus species used for MRI in these fields. The system should not interfere with common commercial Bluetooth and other common radiofrequency patient physiologic telemetry systems used during MRI. (9) The system should be safe for operators and patients inside and near the magnet bores.

The sponsoring NIH laboratory will provide access to acquire physiological signals without preprocessing; alternatively the offeror should have access to such a laboratory independently for development and for testing.

Deliverables

The Phase I proposal is a working prototype to support investigational X-ray and MRI guided clinical interventional procedures. This includes 9-10 ECG leads for use in X-ray and at least 4 ECG leads for use in MRI, 1-3 invasive pressure transducer, and hemoglobin saturation.

The Phase II proposal will translate the Phase I findings into a clinical grade system. Enhanced features in Phase II should include 3 or more invasive blood pressure channels; temperature and respiratory gas concentrations; the system should control and acquire non-invasive blood pressure; MRI-safe and X-ray compatible respiratory bellows.

061 Novel Concepts in Safe "Active" Transmission Lines for MRI Catheters

(Fast-Track proposals will be accepted for catheter technologies.
Fast-Track proposals will not be accepted for mathematical simulations.)

Number of anticipated awards: 2

Background

Magnetic resonance imaging (MRI) is attractive to guide non-surgical cardiovascular interventional procedures because it can visualize soft tissue, guide positioning of therapeutic devices, and assess treatment outcome, all without ionizing radiation. Conventional X-ray-based interventional catheters typically contain ferromagnetic materials incompatible with MRI. Materials substitution for MRI compatibility is usually not sufficient to make devices suitably conspicuous under MRI without obscuring nearby tissue. "Active" MRI catheters incorporate

receive and / or transmit coils attached to the MRI system making the catheters highly visible. Unfortunately, most active MRI catheters incorporate long conductive transmission lines, which are susceptible to significant heating during radiofrequency excitation.

Approaches to attenuate heating, such as detuning and decoupling from the RF excitation coil, are hampered by heterogeneous operating conditions including dielectric properties and loading conditions (continuously variable catheter position with regard to skin surface and body coil). Approaches using inline transformers or chokes have proven lossy or bulky. Multi-channel active MRI transmission lines have suffered unfavorable coupling with other active devices or receiver coils.

The objective of this contract topic is to seek engineering solutions to the problem of heating of interventional cardiovascular active MRI catheter devices.

Specifications

Offerors are requested to propose novel transmission line solutions incorporating micro-miniaturized electronics to attenuate heating. Solutions may focus on either intracorporeal or extracorporeal components of transmission lines or both, but consideration should be given to their impact on integrated solutions.

These solutions should contribute to the development of safe and conspicuous MRI catheter antenna technology, exhibiting tip- and whole-shaft conspicuity, and operating at 1.5 and/or 3.0T.

Potential approaches may include: (1) Electromagnetic shielding to prevent interference between coaxial connections (of active MRI catheters to MRI receiver system) and MRI radiofrequency transmission system; (2) Wireless, fiberoptic, or other alternatives to coaxial connections of active MRI catheters to MRI receiver system; (3) Novel conductive materials that can benefit from a “skin effect” such as carbon nanofibers (4) Using parallel transmission of radiofrequency excitation to reduce specific absorption rate during MRI of active MRI catheters; (5) Approaches to allow multiple independent channels without excessive coupling.

Alternative offerings are also sought to provide high throughput mathematical simulation of active MRI catheter transmission lines systems in realistic models of variable human body morphology and dielectric characteristics.

Successful proposals may develop novel technology or may focus on clinical-grade engineering of high-quality solutions. Catheter solutions should conform to ASTM 2182 heating standards.

The sponsoring NIH laboratory will accept device subassemblies to integrate into clinically-relevant guidewires and catheters. Such transmission line subassemblies should accommodate the mechanical constraints of interventional cardiovascular catheters including low-profile (0.014”-0.035”diameter) guidewires and large-lumen low-profile catheters (5Fr diagnostic and 8Fr interventional) with flexibility comparable to conventional X-ray cardiovascular interventional devices. The catheter working Length should be 190-300 cm (guidewires) or 100-135cm (catheters) long. At least one end of each above range is mandatory. Transmission line subassemblies should allow detachment to provide catheter exchange during interventional procedures.

Deliverables

For catheter technology, the Phase I deliverables include (1) Working prototypes for proof-of-concept, with evidence of successful final miniaturization in the target MRI environment; (2) Testing in vitro according to ASTM heating standards; and (3) Catheters or subassemblies suitable for in vivo testing. Phase II deliverables include clinical-grade implementation and miniaturization of sub-assemblies or final assembled products suitable for human investigation.

For mathematical simulations, only Phase I proposals will be considered. The deliverable will be a model system that allows a “sweep” of operating conditions with a broad range of conductive devices; interpatient electrical characteristics; catheter insertion depth, trajectories, and operating positions. The sponsoring NHLBI laboratory will corroborate mathematical simulations with in vivo experiments.

062 Strategy for Finding Cases of Moderate-to-Severe COPD

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I, $250,000 for 6 months; Phase II, $2,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Approximately 12 million Americans have been diagnosed with COPD, and population-based studies indicate that an equal number of other individuals have this disease but have not been properly diagnosed. With recent advances in the treatment of COPD, the identification and treatment of these undiagnosed patients represents a substantial opportunity for improving public health. A workshop convened by the NHLBI in 2008 concluded that systematic efforts to identify individuals with COPD are urgently needed. Nevertheless, there is no established and validated strategy for case-finding in COPD, and research is needed to define the optimal approach and to determine its feasibility, cost, sensitivity, and specificity. Screening tools that would provide baseline data on which to base policy decisions and the conduct of future clinical trials are needed. Materials and tools applicable to the general population and for use in community practices which often do not have the resources of larger hospitals or academic institutions, are particularly relevant. **The ultimate goal is to design a peak-flow and questionnaire combined tool, and validate it so that it can be offered to the public as an open-source product.**

Tools are not limited to, but should include:

- Design of a questionnaire targeting the general population that aims at selecting those at enhanced risk of COPD.
- Combine the questionnaire with a peak flow measurement in individuals at risk to identify those with significant abnormality of ventilation, so that these can be referred for physician evaluation and diagnosis.

Phase I research is expected to focus on development of a peak-flow and questionnaire based strategy, to provide initial testing of the prototype and demonstrate how it will improve COPD case finding.

Phase II studies should further refine the technology or strategy and validate its effectiveness in community settings in terms of feasibility, cost, sensitivity, and specificity.

063 Reagents for Studying Human Lung Cell Biology and Cellular Function

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4-6

Approximately half of the 44 cells that comprise the human respiratory tract still remain partially identified and their function(s) is incompletely understood (Franks et. al. Proc Am Thorac Soc 2008; 5: 763-6)). Suitable technologies are available to identify, sort, purify, culture, and determine cell surface markers or other unique identifying features that permit individual characterization of cell types. It seems feasible to unravel the origins and functional capabilities of lung cells involved in developmental stages of lung growth and in disease. But it will be necessary to generate new reagents that will identify these still incompletely characterized cells in the human lung, permit establishment of cell lines, and facilitate ready isolation from lung tissue.

Much is known already about many important cells in the human respiratory tract, but little is known about the supportive function of structural cells, the para-endocrine effect(s) of lung cells, and the location and functions of stem and progenitor cells that remain quiescent until stimulated to help repair tissue after injury or disease. Cellular functions that suppress or create apoptosis to reestablish normalcy need insight. Several examples are offered representing the three main compartments of the lung:

1. Among airway cells comprising the large and small airways of the human bronchial tree, the ciliated, columnar, secretory, and basal cells have been well studied, but more knowledge about epithelial stem and progenitor cells along the airways, mucus and ciliated cell interactions, functions of brush cells, and the stimuli from neuro-endocrine cells to affect integrity of the epithelium, all are needed.
2. In the alveolus, information is considerable about Type I cells, the multiple tasks of Type II cells, and surfactant production and properties, but Type II cell stimulated epithelial to mesenchymal transition is evolving but is not understood as a process leading to lung fibrosis, and the activity of interstitially located fibroblasts to secrete extracellular matrix needs more scrutiny.
3. The vascular bed of the pulmonary circulation needs study of the endothelial cells populating different locations and the capillary network, and interactions of endothelium with smooth muscle cells and with adventitial fibroblasts need examination.

Thus, special reagents are needed for studying lung cell biology and cells involved in organ development, growth, and disease. Examples of needed reagents include:

1. Antibodies that will recognize specific cell types and permit separation and recovery of cells from micro-dissected lung tissue.
2. Reagents to identify proteomic products produced by cells.
3. Antibodies that recognize cell surface markers that can help identify and track different cell lineages present in airway and alveolar structures.
4. Specific antibodies to recognize cell surface markers that help to separate out individual cell types from among heterogeneous lung tissue cells.
5. Create reagents that track cellular changes in differentiation as development occurs, track cells that enter latency, and detect signals of re-stimulation or redeployment for repair tasks.
6. Reagents that characterize and identify “stem” and progenitor lung cells.

Phase I proposals should focus on development of reagents that identify unique cell surface markers or other special structures that would permit extraction of cells, considered to be incompletely characterized or identified, from human lung tissue biopsy specimens, or other lung bio-specimens such as transbronchial biopsy and bronchoalveolar lavage. This should lead to cell separation and establishment of in vitro cell cultures.

Phase II proposals should focus on scale up production of unique reagents for cell separation that can be placed in a repository for use by other investigators by application to investigate lung disease, and to study cell proteomics and other functions.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The NIAAA supports research on the causes, prevention, control, and treatment of the major health problems of alcohol abuse, alcoholism, and alcohol-related disorders. Through its extramural research programs, the NIAAA funds a wide range of basic and applied research to develop new and/or improved technologies and approaches for increasing the effectiveness of diagnosis, treatment, and prevention. The NIAAA also is concerned with strengthening research dissemination, scientific communications, public education, and data collection activities in the areas of its research programs.

This solicitation invites proposals in the following areas:

042 Interventions to Prevent and Treat Substance Abuse Among Children, Adolescents and Adults with FASD

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Children, adolescents and adults on the FASD spectrum are at especially high risk for substance abuse and dependence. Use of alcohol and/or other substances can seriously exacerbate the negative outcomes caused by the many disabilities present in this subgroup. Although recent research on interventions targeting certain disabilities common in FASD individuals has been encouraging, virtually no prevention or treatment research addresses substance abuse in this vulnerable population.

It is well known that neurological damage to the developing fetus often occurs in the offspring of women who drink alcohol and/or use other drugs during pregnancy. Alcohol is the leading known preventable cause of mental retardation and other neurobehavioral disabilities. The damage to cognitive, neurological, and physical development is manifest across a wide spectrum of severity, hence the term Fetal Alcohol Spectrum Disorder (FASD). These abnormalities include growth deficiencies, neurodevelopmental delays, diminished intellectual ability, and behavioral and social problems. At the most severe end of the spectrum, individuals with Fetal Alcohol Syndrome (FAS), have characteristic facial dysmorphology, significantly retarded physical growth (both of which may become less obvious with maturity) and severe, lifelong cognitive and behavioral deficits. It is estimated that 1 in 1000 live births in the US are of children with FAS, while 1 in 100 births are children along the spectrum of severity, who are often not identified readily because the characteristic facial features are absent. Most children on the spectrum have a normal life span, although it is unknown how many adults in the population are affected.

Intellectual capabilities vary, with some having an average IQ. But the specific cognitive and neurodevelopment deficits that may result include diminished IQ, learning disabilities and specific language and/or math disorders, attention and information processing difficulties, including ADD and ADHD, perceptual impairments, diminished executive function, and poor learning and memory skills. Further adding to these handicaps are notable problems in social interactions, poor judgment, inability to learn from experience and lack of insight for the consequences of actions. A host of secondary disabilities result from these primary disabilities, including failure in school, psychiatric complications (such as depression), social isolation, susceptibility to victimization by deviant peers, alcohol and substance abuse, entry into the juvenile and adult justice systems, unemployment, inappropriate and/or dangerous sexual behavior, and homelessness. FASD children born into substance-abusing families often receive deficient parenting and ultimately enter the social services system, and experience multiple foster home placements or institutionalization. Some children are adopted into families who may or may not be aware of their child's special needs. Studies have shown that there is a higher prevalence of FASD among certain populations, including those in the juvenile and adult justice system, adoptees and other persons from countries with high substance dependence rates, Native Americans, and children in the foster care system.

In recent years, new interventions aimed at improving functioning and life skills have begun to emerge, some with promising results. However a great deal of additional work is need to develop and validate interventions and incorporate these services into the wide variety of settings where individuals with FASD can be identified. Notably absent from this research are interventions for alcohol and other drug abuse. Adolescents and adults with FASD are at especially high risk for substance abuse, and are unlikely to seek treatment, or to benefit from traditional forms of therapy.

The objective of this contract topic is to develop evidenced-based programs with the capacity to engage, inform, teach and reinforce skills to avoid substance use. Such programs need to specifically targeted to subgroups across the life span and capable of being delivered in a variety of settings, including those where special education professionals may not be available. Modularized programs that can be readily incorporated into larger interventions for FASD persons, such as those that teach social skills, safety, and other life skills are appropriate for this topic. Methods of teacher training, and development of curriculum materials and tools will also be considered. Programs should take into account that many along the FASD spectrum also have co-occurring psychiatric conditions.

043 Medications Development for the Treatment of Alcohol Use Disorders and Alcohol-Induced Tissue Damage

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Efforts to develop medications for alcohol use disorders have expanded rapidly in recent years. Three agents—disulfiram, naltrexone, and acamprosate—are now approved for use in the United States and many other countries. Recently, topiramate also has been shown to be effective in treating alcohol-dependent patients. However, because of the heterogeneous nature of alcohol use disorders, many patients have limited or no response to these medications. Therefore, developing new medications and evaluating their use in combination with other medications and with behavioral therapies are important steps toward improving treatment outcomes for all individuals with alcohol use disorders. A variety of new compounds are being investigated in clinical trials, including gabapentin, ondasentron, levetiracetam, quetiapine, baclofen, zonisamide, pregabalin, prazosin, and kudzu.

Alcohol-seeking behavior and drinking are influenced by multiple neurotransmitters, neuromodulators, hormones, and intracellular networks. Thus, there are many potential targets for drug development. Research to date has focused on opioid, serotonin, dopamine, glutamate, and gamma-aminobutyric acid (GABA); cannabinoids, corticotrophin-releasing factor (CRF), nicotine, adenosine, and neuropeptide systems (e.g., neuropeptide Y); signal transduction pathways (e.g. protein kinase A and protein kinase C); and gene transcription factors (e.g., delta fos B and cAMP response element-binding protein [CREB]). Efforts to define different elements of addiction include reward and motivation, negative effect, cue conditioning/craving/ wanting, disinhibition/impulsivity/compulsivity/habituation, memory, executive function/cognitive function, and interoception/self-awareness. It is important to identify the neurocircuits underlying these elements and investigate their interactions and integration. The ultimate goal is to target specific sites in these neurocircuits with compounds that modulate them.

Advances also have been made in understanding the mechanisms of alcohol-induced tissue damage. Oxidative stress and inflammation play a major role in the pathogenesis of alcohol-associated injuries of various organs, including the liver, pancreas, heart, lungs, brain, and peripheral nervous system. Potential therapeutic agents include those that attenuate the actions of pro-inflammatory cytokines (e.g., the tumor necrosis factor (TNF-α), and antioxidants (e.g. S-adenosyl-L-methionine (SAMe), glutathione, and vitamins A and E). Other potential new treatments of alcoholic liver disease include cannabinoid CB1 antagonists and CB2 agonists, metformin (an insulin-sensitizing agent), antifibrotic agents, prebiotics, probiotics, and zinc.

Finally, to improve safety, efficacy, and efficiency of medications, it is important to identify and characterize patients who respond positively to the medications and those who experience adverse events. Progress in personalized medicine includes evaluating polymorphisms of the mu opioid gene, such as A118G, which appears to modify responses to naltrexone, and the L versus S allele on the serotonin transporter gene, which may influence responses to ondansetron. These and similar discoveries may someday enable clinicians to tailor treatment to the biological profile of individual patients, and thereby to achieve better treatment outcomes.

Specific areas of research include:

- Discover, develop, and test new, more effective agents to prevent or reduce drinking.
- Discover and develop medications to reduce smoking in alcohol-abusing individuals.
- Discover and develop novel medications to treat alcohol-induced organ damage by attenuating or reversing the tissue damage. Identifying new targets for drug development based on mechanisms underlying the alcohol-induced damage is encouraged.
- Advance personalized medicine by employing approaches of pharmacogenetics, sophisticated modeling of human characteristics, brain imaging and physiological and biochemical markers.
- Evaluate combinations of medications to increase efficacy with minimal side effects.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

122 Tool Development for New or Improved Capture Reagents

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $200,000 for 6 months; Phase II: $1,500,000 for 4 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

NIDA seeks proposals to begin to establish a library of protein capture reagents for addiction-relevant proteins and their variants. Relevant proteins would include membrane proteins such as receptors, transporters and ion channels as well as signaling proteins, transcription factors and other nuclear proteins.

Phase I will be to develop new and improved in vitro technologies to generate renewable protein capture reagents that have the potential to specifically or selectively recognize, bind and “capture” proteins and distinguish their natural variants [splice variants, post- translationally modified variants (e.g., glycosylation, phosphorylation, acetylation, oxidation, etc.)]. Initial feasibility will be demonstrated by development of selective reagents for 10 addiction-relevant proteins including variants of those proteins.

Phase II will cover development of selective reagents for 100-200 addiction- or neuroscience-relevant proteins including variants of those proteins.

123 Development of Alternate Drug Delivery Dosage Forms for Drugs Abuse Studies

(Fast track proposals will be accepted.)

Number of anticipated awards: 1

NIDA seeks to design and develop alternate dosage forms of drugs that are not orally administered (such as nicotine and marijuana) for conducting addiction-related research.

The small business companies are invited to submit proposals to develop and test alternate to smoking dosage forms of nicotine and/or marijuana such as deliverable through oral, nasal and/or mucosal routes. Such drug delivery dosage forms, once developed, should be tested and evaluated for efficacy.

In Phase I, the contractor should demonstrate the feasibility of the developing such dosage forms and in phase II the contractor should develop and test the innovative dosage forms.

127 Improving Measures of Addiction Risk

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Drug addiction is a chronic, relapsing brain disease characterized by such cardinal behaviors as compulsive drug seeking and use despite harmful consequences. Individual differences in risk for drug addiction are often expressed in degree rather than kind, that is, as gradations along an underlying continuum that stretches from unobservable variations in risk for addiction to extreme and fully debilitating addiction severity. Assessment instruments in use today for measuring drug addiction (i.e., compulsivity in seeking and using drugs despite harmful consequences) have proven reliability and validity, but are of limited use for evaluating individual differences in *risk* for drug addiction. Advances in computerized adaptive testing methods, computer-assisted technologies, and psychometrics, including item response theory, suggest that the capabilities now exist for the development of the next generation in addiction assessment.

This contract topic is for the development of new assessment instruments to detect meaningful variation between, within, and across individuals over time. Such instruments should be scalable along the dimension of risk for addiction and cover the addiction severity distribution. They should allow for efficient assessment of the liability (risk and severity) constructs, be valid in both sexes, and provide scales that are invariant of the population, with minimal burden for administration, training, and cost to the researcher, clinician, research participant, or patient. Finally, they should provide valid and reliable scores corresponding to established diagnostic criteria for substance use disorders.

128 Video Game Targeting Relapse Prevention in Youth with Substance Use Disorders

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Number of anticipated awards: 1

Despite advances in the development of treatments for adolescents with substance use disorders, relapse remains to be a concern. This contract topic will support research to develop a video game targeting prevention of relapse for youth with substance use disorders. Video game platforms of interest include computers, handheld devices, and video game consoles. The video game can be used as a single modality or as part of a continuing care program. Phase I will support the development and feasibility testing of the video game for use with adolescents with substance use disorders. If feasible, Phase II will support further development based on Phase I findings, and pilot testing of efficacy in post-treatment adolescents. The proposed project should be theory based and designed to assess the hypothesized mechanism of action of the intervention (e.g., maintenance of skills learned in treatment or motivation to abstain). This innovative technology is intended to attract and engage adolescents in programs designed to maintain treatment gains and prevent relapse.

129 Developing Implementation Packages for Evidence-based HIV Prevention Intervention Materials for Drug Users

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

The purpose of this SBIR contract topic is to increase the availability of evidence-based interventions (EBIs) for prevention of HIV acquisition or transmission among drug using populations and the settings that serve them. The CDC Compendium of Evidence-Based HIV interventions http://www.cdc.gov/hiv/topics/research/prs/evidence-based-interventions.htm provides the range of applicable interventions. The settings of interest include health care or public health clinics, community based organizations, social service agencies, mental health or drug treatment settings, syringe and needle exchange programs, or criminal justice settings, with particular emphasis on the kinds of settings that receive state or federal funding for HIV prevention and which are expected to use EBIs as a condition of funding.

Despite the utility of the compendium, and the existence of numerous EBIs, what is lacking is completed and tested packages associated that can enable front-line service providers in these settings to deliver the interventions with consistency and fidelity to the core elements of the interventions. As such, this contract topic seeks the development of “resource packages” that include an implementation manual about the following features of the EBIs:

a. content and delivery method;
b. rationale and scientific basis of the intervention
c. the need for fidelity in the delivery of the intervention’s core elements
d. methods for engaging stakeholder support; and guidelines for preparing implementation (e.g., cost estimation, facility and capacity issues, engagement/retention, monitoring of implementation and outcomes)
e. guidance for integrating the intervention into routine delivery of services to drug using populations.

The resource package to be developed should be accompanied by a training and technical assistance manual so that master trainers or capacity building assistance providers can effectively train agencies and service providers to integrate the EBI into routine practice, with particular attention to providing fidelity and effectively monitor its uptake and delivery in order to improve program outcomes. All levels of evidence in the compendium are considered acceptable, although preference may be given to those meeting "best evidence" criteria, as defined by CDC. It is expected that responses to this solicitation will focus on a single intervention for packaging.

130 Developing, Validating, Refining Tools for Ecologic Momentary Assessment

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Ecologic Momentary Assessment (EMA) is broadly defined as the measurement of exposures and events in real time as they occur, and in the natural environment where they occur, such as the home, neighborhood, or workplace. EMA tools include a wide range of portable technologies for longitudinal data collection in the field, such as electronic diaries embedded in mobile phones and PDAs, geopositioning devices, motion sensors, biosensors, environmental sensors, and audiovisual devices. In addiction and behavioral research, new EMA tools may enhance the contextual and temporal resolution of exposures, and the biological or behavioral processes presumed to occur in response. However, numerous challenges remain for widely implementing EMA in etiologic and intervention research, including optimizing the timing of measurement and data quality, establishing sensor validity and reliability in different populations, reducing intensely longitudinal data for statistical analysis, achieving user acceptability, and safeguarding user privacy. For this contract topic, studies are encouraged that address these challenges and other challenges to improve the validity and acceptability of EMA tools. These studies should identify the development of new tools, or to more appropriately test existing tools, that use EMA.

131 E-Technology Tools for Extending the Reach of Prevention Interventions in Rural and Remote Locations

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

This contract topic is intended to stimulate development of new technologies for delivery and implementation of efficacious drug abuse prevention interventions for rural and frontier communities. Historically, rural communities have experienced lower rates of substance use, HIV/AIDS and risk behaviors compared with other geographic areas. However, studies show increasing levels of substance use, high risk behaviors, and rates of HIV/AIDS in rural areas, particularly in the south. Recent research findings provide evidence that substance use is similar, and, for some substances, greater in rural areas compared with urban and other areas. Higher rates of alcohol use, stimulant and methamphetamine use have been observed among youth in rural areas compared with youth in urban areas. Adults in rural areas were more likely to use methamphetamine and reported higher rates of tobacco use. Though the HIV/AIDS epidemic emerged in urban areas, it has spread and has become prevalent in rural areas. In 2003, 7.6% of reported AIDS cases were in rural areas, up from 5% in 1995.

Though evidence based prevention programs and interventions exist, there is a gap in adequate prevention programs and strategies designed for and to reach rural populations and communities. A number of factors make availability, delivery and implementation of prevention programs challenging in rural areas, including poverty, lack of community resources, limited insurance coverage, lack of funding for prevention programs/services, scarce availability of social and behavioral health services, lack of recreational facilities, logistical difficulties resulting associated with transportation, geographic isolation, and climatic conditions, cultural differences, and concerns about confidentiality and social stigma.

SBIR contract proposals submitted under this topic should propose development of technological tools/products to address the barriers that limit, and/or hinder access to, implementation and delivery of prevention interventions to individuals in rural locations. Technologies might include, but are not limited to, telehealth tools utilizing various forms of technology (e.g. mobile and wireless technologies); computer and mobile devices for delivering

interventions/messages and tracking behaviors; web-based drug abuse prevention interventions that do not require frequent in-person visits (e.g., interactive websites, video linkages, asynchronous linkages with moderated chat rooms); technologies to enable remote access (e.g., telemedicine tools); and, centralized monitoring of behavioral, physiological and other indices.

132 Development of a Device for Auto-administering Naloxone to Overcome Overdose

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Opioid addicts are prone to overdose on injected opiates or on excessive oral doses of opioid medications. These incidents often occur in private settings where no one is present to offer assistance and the addict succumbs to the overdose. Such an event can also occur among patients who are properly medicating for pain, such as in end-stage cancer pain or other unremitting serious pain. To counter inadvertent excess opioid dosing, whether in such patients or in "street" addicts, the proposed research intends to develop and test an automated device that would administer standard doses of naloxone based on the patient's physiologic signal (eg hypoxia, respiratory rate falling below a critical threshold for a critical period of time, etc). The unit would be capable of repeating the injection if necessary, after resetting itself and detecting another set of critical information. The potential market includes non-addicts who are maintained on high-dose opioids for pain, as well as opioid/opiate addicts, especially those who are maintained on methadone and who may experience overdose if attempting to provide added opioid effects through use of illicit opioids or heroin by injection.

133 Development of a Device to Assess Hyperalgesia at the Bed Side by the Cold Pressor Test

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Opioid-induced-hyperalgesia (OIH), as revealed by the cold-pressor test, occurs in a significant segment of opioid-exposed patients and may have critical clinical implications. The increased sensitivity to pain and diminished response to opioid analgesia often means much higher analgesic requirements for post-operative pain control. The cold-pressor test appears to involve overlapping, neuronal circuitries similar to those involved in neuropathic pain, and may thus be especially pertinent for use in managing pain for these patients. Unfortunately the available technique for detecting hyperalgesia with the cold-pressor test is a cumbersome process unsuited for use at the bed side. The traditional technique involves a large basin of ice-water maintained at a near freezing temperature with chillers and mixing equipment to ensure consistent measurements, and a closely monitored procedure of preparation, submersion, and removal of a patient's elbow from the water. A portable test with equipment that can be used at the bed side, in out-patients clinics and physicians' offices, would greatly facilitate research and clinical application of the detection of hyperalgesia. The goal of this contract is to develop and test an electrically operated device capable of inducing and detecting cold--pressor type pain. The equipment and procedures to be developed would have promising market potential in the increasingly prevalent clinics and physicians' offices that are becoming sites of treatment for opioid-abusing patients, including pain patients who have become dependent on increasing levels of opioid medications.

134 Screening, Characterization and Validation Assays for Protein Capture Reagents

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $200,000 for 6 months; Phase II: $1,500,000 for 4 years

It is strongly suggested that Proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

NIDA seeks proposals to develop and validate methods to characterize protein affinity reagents and to establish standard operating procedures for those methods.

The utility of protein affinity reagents is greatly enhanced by information regarding in situ or in vitro binding conditions, effects of post-translational modifications of the protein target on reagent binding, reagent selectivity and stability.

Phase I of this SBIR will be development and validation of methods for such characterization. Part of Phase I will also be development of standard operating procedures. It is important that methods developed can be implemented for high throughput screening of affinity reagents.

Phase II will use methods and SOPs developed in Phase I to characterize commercially available affinity reagents. The characterization data and appropriate metadata will be made publicly available.

135 Development of New Methods and Approaches to Monitor Medication Compliance in Clinical Trials

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Low medication compliance is a major problem in the conduct of clinical trials. Moreover, low compliance to marketed medications in the US has been estimated to result in a cost of at least 100 billion dollars and 100,000 deaths each year. In clinical trials, low medication compliance poses a different but equally serious problem. Thus, variations in compliance during the course of a clinical trial can alter clinical outcomes, often masking a therapeutic effect. This can result in the failure to develop potentially effective medicines, or result in additional cost and delay in the drug development cycle. Investigators in clinical trials have used numerous methods to assess patient compliance with medication regimens to try and identify noncompliant subjects. Numerous publications document a variety of methods and approaches to measure noncompliance and/or to improve medication compliance. Some of the methods are based on the measurement of drug levels in blood or urine samples, measurement of nontoxic biomarkers such as riboflavin in urine, self-reporting, pill counts, use of electronic monitoring devices, etc.

Development of medications for drug abuse/drug addiction, evaluation and selection of safe and effective medications, through clinical trials, is an important object for NIDA. Accurate monitoring and measurement of compliance will help NIDA determine the safety and efficacy of medications in clinical trials. NIDA is soliciting SBIR contract proposals to develop practical and efficient methods/approaches, with reasonable cost, to assess medication compliance in clinical trials. Examples of new methods could include, but are not limited to, the use of nontoxic isotopic labeled excipients, new techniques in nanotechnology for electronic monitoring (either in vivo or externally), monitoring through transdermal patches or implants, or monitoring metabolites through external monitors.

In Phase I, the contractor will evaluate the practical feasibility of the methods/approaches.

In Phase II, the contractor will demonstrate that the methods/approaches can reliably assess compliance in clinical trials.

136 New Techniques for the Large Scale Production and Purification of Antibodies or Vaccines for the Treatment of Substance Use Disorders

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Phase I proposals of one year will be accepted.

The National Institute on Drug Abuse (NIDA) seeks Small Business Innovation Research (SBIR) contract proposals for innovative new immunotherapeutic production methods. The discovery and development of immunotherapies such as monoclonal antibodies (mAbs) and vaccines are currently being explored as safe and

effective means to treat various aspects of substance use disorders including phencyclidine and methamphetamine drug overdose, as well as relapse prevention of cocaine abuse and nicotine dependence.

Because of these advances, there is a need for: 1) bulk scale production of new antibodies/vaccines in quantities large enough for clinical trials and 2) the design and implementation of clinical trials using immunotherapy for treatment of substance abuse disorders.

Thus, specific areas of interest include:

- Alternative methods to antibody and immunoconjugate production that minimize contamination problems (such as animal proteins and viruses, and culture media constituents) or avoids them altogether;
- Innovative/alternative methods of antibody production that provide faster and more efficient manufacture and involves less toxicity testing;
- New immunotherapeutic purification methods that maintain high yields;
- New technologies in proteomics to facilitate more rapid and efficient production methods.

All methods proposed should be for the production of immunotherapeutic vaccines or antibodies either developed or under development for the treatment of substance use disorders and is/will be suitable for GMP production.

In Phase I, the contractor is expected to explore techniques and approaches for large scale production of a vaccine or monoclonal antibody and demonstrate the feasibility of applying the techniques and approaches to the large scale manufacture of the immunotherapy agent. In Phase II, the contractor is expected to select and develop the most efficient technology/approach and establish procedures for GMP scale-up production.

137 Rapid Portable Devices to Measure Drug Use

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

NIDA's International Program supports efforts to advance NIDA's research agenda and to foster the development of research capacity internationally by taking advantage of unusual talent, resources, populations, or environmental conditions in other countries. To facilitate these efforts, NIDA's International Program is interested in supporting US-based small businesses to develop products and services in the following area:

Development of valid, reliable, and standardized test instruments and devices that could be used in studies of drug use and their effects. Of particular interest are efforts to develop improvements in techniques and devices, such as cell phones, in the collection of epidemiological data on drug use patterns. Also of interest are efforts incorporating measures of behavioral, physiological, and/or toxicological effects of drug use related to driving behavior. Instruments and devices should be amenable to roadside use. Such instruments and devices will be useful in studies to determine which substances impair driving-related behaviors, and will be useful in international comparative studies of drugged driving and in the establishment of improved consumer advice and product regulation.

138 Real-time Activity as a Potential Diagnostic Marker for Pain or Drug-craving

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Characterization of drug dependence (especially drug craving) and pain has relied on subjective self-report measures of symptomatology. In addition to individual differences in the actual brain signal instantiation of craving and pain, the translation of these internal states into an overt reporting format introduces an additional layer of variation into analysis of outcomes. Of interest are contracts to explore direct brain endophenotypic markers of pain, craving, or other addiction severity. Functional magnetic resonance imaging (fMRI) has characterized limbic

brain recruitment patterns characteristic of either craving or pain in the form of static contrasts between discrete brain states. However, to date, these reports have merely detected group-mean differences in signal in certain regions, where brain signal has not been predictive of clinical group status of individual subjects. Improved image analysis and reconstruction hardware, however, have now enabled dynamic brain-wide pattern recognition and classifier training with real-time fMRI data collection. This has now enabled "brain-reading," where for example, a classifier can be trained to distinguish what hand motion a subject is performing, or even what word a subject is contemplating.

NIDA is interested in contract proposals seeking to apply real-time fMRI-based or EEG-based brain-reading to pain and drug-abuse-relevant mental states. Phase I would focus on obtaining preliminary characterization of pain or addiction-related brain states in real time using brain-wide pattern recognition. Phase II would center on: a) improvement of this pattern recognition into a generalizeable classifier of pain- or addiction-related brain state, and b) application of the brain-state classifier to a novel set of human subjects to ascertain its predictive validity (on an individual-subject level) of diagnostic severity, prognosis for treatment, and tracking of recovery after therapy.

139 Confirming Compliance with Experimental Pharmacotherapy Treatment of Drug Abuse

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Assessing the results of clinical investigations of pharmacotherapies for treating drug abuse is made difficult by the lack of certainty that patients have taken the prescribed treatment as instructed. Negative outcomes of trials of pharmacotherapies might be due to the failure of the product, or might be due to the failure of patients to comply with the treatment. Patients in clinical trials of medications for treatment of drug abuse might be motivated to not take the prescribed medication if they preferred to continue abusing drugs. If the patient chose to get “high” by abusing drugs, the experimental medication could interfere with the desired effects of the abused drug. The same patient might then be motivated to continue as a patient in the trial, and so report to the clinical staff that they have regularly and faithfully taken the medication as prescribed, when they have not complied. NIDA seeks to overcome these situations and accurately determine whether or not medications are used as instructed. Proposals are sought for technologies/products that can allow clinical staff to determine compliance with medication regimens. The technologies/products should allow patients to take experimental medications by the oral or subcutaneous routes not in the presence of clinical staff members (e.g. at home). Use of such technologies/products should provide clinical staff with greater certainty regarding compliance than that derived from patient self-report or from counting unused pills or medicated skin patches.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. This Small Business Innovation Research Program (SBIR) uses a combination of research and technology transfer in order to develop new products that will aid the mission of NIEHS.

This solicitation invites SBIR proposals in the following areas:

113 Application of ‘Omics' Technologies to Rodent Formalin-Fixed, Paraffin Embedded Tissue Samples

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: $150,000 for 1 year

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

The National Toxicology Program's Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused on target-specific, mechanism-based, biological responses. Thus, the NTP is placing an increased emphasis on the use of alternative assays for targeting key pathways, molecular events, or processes linked to disease or injury, and has established a High Throughput Screening (HTS) program, representing a new paradigm in toxicological testing. One of the most effective ways of evaluating relationships between molecular pathways identified from studies using cultured cells exposed to environmental agents and the ability of the same agents to induce disease is through the use of 'omics technologies on tissue samples obtained from in vivo toxicity studies. The NTP maintains one of the largest repositories in the world of formalin-fixed paraffin embedded (FFPE) tissue samples collected from nearly every GLP toxicity study carried out by the program over its 30-plus year history. Detailed pathology has been performed on all samples in the repository accompanied by serum chemistries and observational measures; however, very little is known about the molecular-level changes that parallel the pathology observed in these tissue samples. Recent technical developments allow for the successful extraction of DNA, RNA, or protein from FFPE samples for use in low dimensional molecular biology analyses. However, methods for the global assessment of changes related to these macromolecules are only starting to be developed. **The purpose of this SBIR topic is to support the development of methods and tools that enable the use of FFPE tissues for Next-generation sequencing analysis of the genome, transcriptome, and epigenome.** Effectiveness of developed methods will be determined by comparison to data generated using fresh frozen tissue.

114 High Throughput Screening for Reactive Oxygen Species Mediating Toxicity

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: $150,000 for 1 year

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

The National Toxicology Program's Vision for the 21st Century is to transform toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon target-specific, mechanism-based, biological responses. Thus, the NTP is placing an increased emphasis on the use of alternative assays for targeting key pathways, molecular events, or processes linked to disease or injury, and has established a High Throughput Screening (HTS) program, representing a new paradigm in toxicological testing. The NTP is using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. The goals of this HTS program are to prioritize substances for further in-depth toxicological evaluation; to identify specific mechanisms of action for further investigation; and to develop predictive models for in vivo biological response. It is well known that the generation of reactive oxygen species (ROS) produced by chemical exposure can damage DNA, protein and lipids resulting in a variety of pathologies. Relevant species include hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), singlet oxygen ($^1O_2$), superoxide anion ($O_2^{\cdot-}$), hypochlorite anion (^-OCl), peroxyl radicals (ROO•) and others. Although superoxide dismutases, catalases and peroxidases are usually efficient defenses against ROS, these defenses can be overwhelmed, resulting in measurable ROS accumulation and toxicity. **This SBIR topic solicitation is intended to support the development of quantitative high throughput or high content screening methods for the detection of various reactive oxygen species generated by some environmental toxicants.** The methods may either generally detect ROS or selectively detect particular oxygen species. Linkage of ROS generation to specific subcellular organelles, to specific macromoleular effects such as protein or DNA damage, or other biological or toxicity endpoints is encouraged. Inclusion of positive controls for ROS assays that show assay detection limits and specificity are needed. These assays will be conducted at the NIH Chemical Genomics Center (NCGC) using a robotic platform that imposes specific requirements on the experimental design that can be employed in the quantitative high throughput screens conducted there. The experimental design requirements are described in detail at

http://www.ncgc.nih.gov/guidance/HTS_Assay_Guidance_Criteria.html. Screens developed must meet these requirements.

115 In Vitro 3D Tissue Models for Toxicity Testing

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: $150,000 for 1 year

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

The National Toxicology Program (NTP) Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. Thus, the NTP is placing an increased emphasis on the use of alternative assays for targeting key pathways, molecular events, or processes linked to disease or injury, and has established a High Throughput Screening (HTS) program, representing a new paradigm in toxicological testing. However, significant limitations of this approach are that it focuses on acute exposure conditions and ignores the complexity of the multiple cell type interactions that occur in vivo in tissues/organs. **This SBIR is intended to support the development of in vitro experimental systems capable of replicating major organ systems in humans, to be used for increased throughput and high data content screening of the mechanistic and toxicological effects of potential environmental toxicants.** An emphasis is on developing systems that replicate key functions associated with skin, kidney, and lung that are most relevant to environmental health. In terms of skin, the goal is a fully stratified three-dimensional skin model for dermal irritation and corrosivity testing. Therefore, the model should consist of dermal and epidermal compartments recapitulating the tissue architecture and barrier function of interfollicular epidermis, and allow for the paracrine signaling seen *in vivo*.

These engineered tissues can be generated using biopsy, explanted, or excess transplant tissue or differentiated human stem cells and therefore the screening systems should be more relevant to human health than models based on experimental animal tissues. The 3D tissue model should be amenable to (1) 'omics technologies to identify biomarkers of exposure and response, including biomarkers at the pathway and network level, and (2) strategies for manipulating the genetic background of the culture system to study alterations in susceptibility to environmental factors resulting from genetic variation. Where appropriate, the sensitivity and specificity of these tests should meet or exceed current standards animal models used for regulatory testing.

116 Development of Improved Biomarkers as Earlier Humane Endpoints for Ocular Safety Assessments

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: $150,000 for 1 year

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Determination of the potential for new chemicals and products to cause adverse health effects is necessary to provide for the protection of human health. Information from ocular safety testing is used to determine appropriate precautions necessary to protect workers and consumers, to ensure proper hazard labeling and safe packaging, and to provide information regarding appropriate treatment of accidental chemical exposures and injuries. While *in vitro* methods have been developed and accepted to identify severe and corrosive ocular injuries, safety evaluations of new chemicals to assess whether chemicals may cause reversible injuries is still required in most situations. However, the current endpoints in these methods are subjective visual observations. These tests can involve unrelieved pain or distress and require prolonged observation periods to determine if the damage is reversible or permanent. The National Toxicology Program is charged with developing and validating improved

testing method for acute and chronic toxicity testing, including alternative methods that reduce, refine, and replace animal use. **The objective of this project is to develop innovative methods that: 1) incorporate new technologies and mechanistic biomarkers that will provide a more reproducible, objective, and sensitive assessment of ocular injuries; 2) provide earlier and more accurate prediction of reversible versus irreversible damage; and 3) can be used as earlier humane endpoints for early termination of studies to avoid continued potential pain and distress without interfering with the predictivity of the test.** Technologies that might be applicable include the use of ultrasound imaging, reflectance colorimetry, biomicroscopic/slit-lamp evaluations, confocal microscopy to assess depth of corneal injuries, pachymetry to assess corneal thickness, or other innovative technologies. Development and validation of these methods should be accomplished using appropriate positive and negative reference substances for the range of toxic effects that the method is expected to detect. Appropriate anesthetics and analgesics should be used to alleviate any expected pain or distress.

117 Development of Sensitive Innovative Methods for Detecting and Assessing Pain and Distress in Laboratory Animals Used in Toxicological Research and Testing

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: $150,000 for 1 year

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Toxicological research and testing is conducted to investigate the mechanisms of toxicity and to characterize the hazard or safety of new chemicals in order to protect and advance the health of people, animals, and the environment. While *in silico* and *in vitro* methods are increasingly being used, many studies continue to require the use of animals to assess complex physiological and behavioral adverse effects from acute and chronic studies. When chemicals induce damage or disease in tissues and organs, this can lead to pain and distress in laboratory animals. Minimizing pain and distress not only improves the welfare of animals, but also improves experimental results by reducing the potential confounding effects of pain. The NIH Revitalization Act directs NIH to conduct or support research into methods of research and experimentation that produce less pain and distress in animals. However, objective and sensitive methods for detecting the presence of pain and distress are needed that can be used as the basis for interventions to reduce or relieve pain and distress and for monitoring the effectiveness of such interventions. **The goal of this project is to identify, standardize, and validate early objective and sensitive biomarkers indicative of pain and distress in laboratory animals used for toxicological research and testing. The project seeks the application of existing noninvasive technologies for measuring behavioral or other physiological changes that are indicative of acute and chronic pain and distress.** Approaches should minimize disturbances to animals such as with the use of remote wireless recording. Objective biomarkers that may be appropriate include remote video recording and analysis of the nature and frequency of postural movements, and alteration in physiological biomarkers such as cardiopulmonary parameters. Studies should provide proof of concept of the extent that the measured parameter is predictive of pain or distress, the extent of reproducibility of the biomarker, and the extent that the marker provides quantitative assessment of the severity of acute and chronic pain or distress.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

The National Center for Chronic Disease Prevention and Health Promotion is leading efforts to promote health and well-being through prevention and control of chronic diseases that all people might live healthy lives free from the devastation of chronic diseases. Priorities focus on well-being, health equity, research translation, policy promotion and workforce development.

Cancer is the second leading cause of death in persons under the age of 85. Two of the most common cancers (breast and colorectal cancers) have evidence-based screening tests available to find these cancers early when they are curable. Screening tests for colorectal and uterine cervix cancer identify precancerous lesions which can be detected, removed and preventing the cancers from developing. Even though knowledge of the benefits of screening for these cancers is widespread, these screening tests tend to be underutilized.

For this solicitation NCCDPHP invites Phase I proposals in the following area:

032 Improving utilization of screening tests for colorectal, breast and cervical cancers

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

NCCDPHP is interested in the development of products to improve the utilization of screening tests for colorectal, breast and cervical cancer. **The goal of this SBIR project is to develop electronic reminder systems and innovative education materials and approaches to assist health care systems and providers to remind men and women that cancer screening is needed.** These interventions should be consistent with recommendations published by The Guide to Community Preventive Services (http://www.thecommunityguide.org/cancer/index.html) and the United States Preventative Services Task Force (http://www.ahrq.gov/clinic/cps3dix.htm#cancer). The major focus is to develop clinical tools and educational materials which can be deployed in health care systems and communities to improve cancer screening for which substantial evidence exists for which the benefits have been clearly shown including colorectal, breast and cervical cancer screening. The projects may address concerns along the early detection continuum including outreach for screening, adherence to screening at recommended intervals, follow-up after abnormal screening test results, diagnosis and treatment of premalignant and malignant conditions discovered. These projects may be developed from the patient, provider or health system perspective. Projects should include plans for dissemination of system components and educational materials once developed.

Acceptable studies include:

- Designing, developing, and evaluating innovative educational materials, including electronic materials and modalities, for the general public and community-based organizations that describe various known and suspected causes of cancer and their common sources and the steps that people can take, both individually and collectively, to reduce exposures, identify safer substitute products, and promote healthier communities.

- Designing, developing, and evaluating innovative educational materials, including electronic materials and modalities, for public health, medicine, nursing and allied health professions to increase colorectal cancer screening.

- Developing technology and tools for personal reminder systems for consumers to better track their cancer screening records and to identify the appropriate timing for specific screening tests, consistent with recommendations and tailored to personal risk profiles (age, sex, family history, medical history). This applies to personal health records.

- Expanding the use of information technology in cancer surveillance, particularly through the use of electronic reporting from health provider's offices to central cancer registries.

- Identifying technology to better understand the management of cancer, in the case of disaster (manmade or natural).

- Developing tools to support effective technology transfer of interventions to increase cancer screening.

- Developing technology to aid in the technology transfer of reminder systems for health professionals to improve cancer screening.

- Developing a performance support tool for health professionals working in cancer prevention and control to rapidly build effective new media strategies. Conduct research and development to build and disseminate web-based interventions for public health and medical professionals working to promote breast, cervical and colorectal cancer screening.

NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP)

The mission of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) is to maximize public health and safety nationally and internationally through the elimination, prevention, and control of disease, disability, and death caused by HIV/AIDS, Viral Hepatitis, other Sexually Transmitted Diseases, and Tuberculosis. Website: http://www.cdc.gov/nchhstp/.

For this solicitation NCHHSTP invites Phase I proposals in the following area:

030 Development of a Non-Invasive Method of Accurate Blood Glucose Determination

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: $150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Over one million Americans have chronic hepatitis B infection that can result in cirrhosis, end-stage liver disease, and hepatocellular carcinoma (liver cancer) in a substantial portion; and an estimated 2,000 US residents die each year wholly or in part due to underlying hepatitis B virus infection. An estimated 43,000 new hepatitis B virus (HBV) infections occurred in 2007 but, while this represents a major decrease in incidence from a decade ago and the growing beneficial impact of infant and childhood vaccination programs, the incidence of HBV in persons over the age of 45 years has not appreciably declined in recent years (CDC Surveillance for Acute Viral Hepatitis-2007. *MMWR* 2009; 58[SS-3]). In fact, the incidence per 100,000 population is roughly the same now for persons above and below 45-years old. An increasing number of outbreak investigations by CDC and state and local health departments have revealed many HBV cases in diabetic elderly persons residing in nursing homes and assisted living facilities (Thompson et al, *Ann Intern Med* 2009; 150:33-9). HBV in elderly persons, especially diabetics who have underlying immuosuppression, is associated with high morbidity and mortality. These persons have limited response to hepatitis B vaccination, so prevention of HBV in them is especially problematic. Most of these outbreaks have been found to be the result of shared glucose monitoring equipment used by staff on several patients. Glucometers and other such equipment may not be cleaned adequately or at all between use on several patients, and hepatitis B may be transferred in blood in the glucose monitoring equipment. Thus, development of a non-invasive-- non-direct blood-measurement-- method of monitoring serum glucose levels would prevent such mechanical transfer of HBV among diabetics in these institutional settings.

The incidence of hepatitis B is falling rapidly, but outbreaks of acute hepatitis B associated with shared glucose monitoring equipment in diabetic residents of nursing homes, assisted living facilities and other institutions have been increasingly detected. As the absolute and proportional numbers of both Americans with diabetes and needing assisted care in such facilities is anticipated to markedly increase in the future, these outbreaks will place an ever increasing burden on the healthcare system. Most of these elderly persons have not been vaccinated and are not aware of their HBV infection; the potential for spread by glucometers and other glucose measuring devices (e.g., requiring lancets) puts these persons at immediate and long term increased risk of liver disease and death.

The goal of this SBIR project is to develop a non-invasive-- non-direct blood-measurement-- method of monitoring serum glucose levels that would prevent the mechanical transfer of hepatitis B virus among diabetics in these institutional settings such as nursing homes or assisted living facilities.

Projects that develop, validate and market a non-invasive glucose monitoring device with the same precision as achieved by standard methods applied to blood samples will be accepted. For example, an approach similar to pulse oximetry, but focused on the glucose molecule, is an example of optic technology that may be commercially feasible. Other non-invasive monitoring approaches—such as reverse iontophoresis, absorption or bioimpedance spectroscopy, and other approaches are also acceptable.

This SBIR proposal offers an opportunity to collaborate with the DVH Epidemiology and Surveillance Branch, DVH, NCHHSTP and the Food and Drug Administration (FDA) focusing on novel ways to measure blood glucose accurately without lancet or other invasive technology, to reduce transmission of hepatitis B, especially in diabetic elderly nursing home and other extended living facilities residents. Collaborations with other Divisions include, but are not limited to, Division of Diabetes Translation (DDT), National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP).

PART II HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

1. INTRODUCTION

A Protection of Human Subjects section of the Research Plan is required for all proposals. The information provided in the section on Protection of Human Subjects should be consistent with the information provided on the face page of the application.

For all research involving human subjects, the Scientific Review Group (SRG) will assess the adequacy of protections for research participants against research risks, and the appropriate inclusion of women, minorities, and children, based on the information provided in the application.

To assist in preparing the section on Protection of Human Subjects, six possible scenarios are provided in Section 2 below. All research projects will fall into one of these six scenarios. Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3 of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, Definitions. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

2. SCENARIOS

Scenario A. No Human Subjects Research

If no human subjects research is proposed in the proposal, check the box marked “No” on the Proposal Cover Sheet (Appendix A) and indicate “No” on the Proposal Summary and Data Record (Appendix G). If your proposed research involves human specimens and/or data from subjects, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

See the instructions for Scenario A.

Scenario B. Non-Exempt Human Subjects Research

If research involving human subjects is anticipated to take place under the award, check the box marked “Yes” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G). Enter your Human Subjects Assurance Number.

In the Protection of Human Subjects section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46), and (2) the requirements of NIH policies on inclusion of women, minorities, and children. Research involving a clinical trial will fall under either Scenario E or F below.

See the instructions for Scenario B.

Scenario C. Exempt Human Subjects Research

If **all** of the proposed research meets the criteria for one or more of the exemptions from the requirements in the DHHS regulations (46.101(b)), check the box marked “Yes” on the Proposal Cover Sheet (Appendix A). Indicate “Yes” on the Proposal Summary and Data Record and insert E-1, E-2, E-3, E-4, E-5, or E-6 as appropriate, in the field for Exemption Number (Appendix G). Leave IRB Approval Date field blank since a Human Subjects Assurance Number is not needed for exempt research. Check “N/A” in field for “example of informed consent” and “Clinical Protocol” as these are not required for exempt research.

In the section on Protection of Human Subjects in the Research Plan, provide a justification for the exemption(s) containing sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate.

The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their website http://www.hhs.gov/ohrp/ for guidance and further information.

The exemptions appear in Part I, Section 3, Definitions.

See the instructions for Scenario C.

Scenario D. Delayed-Onset Human Subjects Research

If human subjects research is anticipated within the period of the award but plans for involvement of human subjects cannot be described in the application as allowed by the DHHS regulations (45 CFR Part 46.118), check "Yes" to "This proposed project involves human subjects" on the Proposal Cover Sheet (Appendix A) and indicate "Yes" on the Proposal Summary and Data Record (Appendix G). In the section on Protection of Human Subjects in the Research Plan, you should either include an explanation of anticipated protections for human subjects or an explanation of why protections cannot be described.

Examples of delayed-onset of human subjects research include:

- Human subjects research is dependent upon the completion of animal or other studies; or
- Human subjects research protocols to be included will undergo an independent decision-making process (often defined by a FOA).

See instructions for Scenario D.

Scenario E. Human Subjects Research Involving a Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct a clinical trial during the project period, check the boxes marked "Yes" on the Proposal Cover Sheet (Appendix A) to "This proposed project involves human subjects," and "Clinical Trial?" Indicate "Yes" on the Proposal Summary and Data Record (Appendix G). In addition, complete the items regarding the Institution's General Assurance, Institution's Review Board, informed consent and clinical protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46);
2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
3) the ClinicalTrials.gov requirements if applicable;
4) the requirements of NIH policies on inclusion of women, minorities, and children; and
5) the requirements of NIH policy on reporting race and ethnicity data for subjects in clinical research.

See instructions for Scenario E.

Scenario F. Human Subjects Research Involving an NIH-Defined Phase III Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct an NIH-defined Phase III clinical trial during the project period, check the boxes marked "Yes" to the following statement/questions on the Proposal Cover Sheet (Appendix A):

- This proposed project involves human subjects.
- Clinical Trial?
- Agency-Defined Phase III Clinical Trial?

Also indicate "Yes" on the Proposal Summary and Data Record (Appendix G) to the following question: Does this proposal involve human subjects research? In addition, complete the items regarding the Human Subjects Assurance Number, Institution's Review Board, informed consent and Clinical Protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46);
2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
3) the ClinicalTrilas.gov requirements if applicable;
4) the requirements of NIH policies on inclusion of women, minorities, and children;
5) additional Requirements for NIH-defined Phase III clinical trials; and
6) the requirements of NIH policy on reporting race and ethnicity data for subjects in clinical research.

See instructions for Scenario F.

3. INSTRUCTIONS FOR PREPARING THE SECTION ON PROTECTION OF HUMAN SUBJECTS

Scenario A. No Human Subjects Research Proposed

Criteria

Human Subjects Research	No
Exemption Claimed	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

Instructions and Required Information

In the proposal narrative, create a heading labeled "Protection of Human Subjects" and include the following statement below the heading: "No Human Subjects Research is proposed in this proposal."

If proposed studies using coded human data or biospecimens do not involve human subjects as described in the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm), provide an explanation of why the proposed studies do not constitute research involving human subjects.

The explanation could include: a description of the source of the data/biospecimens; the role(s) of providers of the data/biospecimens in the proposed research; and the manner by which the privacy of research participants and confidentiality of data will be ensured.

Research that does not involve intervention or interaction with living individuals, or identifiable private information, is not human subjects research (see Part I, Section 3, Definitions).

Research that only proposes the use of cadaver specimens is not human subjects research because human subjects are defined as "living individuals." The use of cadaver specimens is not regulated by 45 CFR Part 46, but may be governed by other Federal, State or local laws.

Scenario B. Non-Exempt Human Subjects Research

Criteria

Human Subjects Research	Yes
Exemption Claimed	No
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct.

In the proposal narrative, create a section entitled “Protection of Human Subjects” and create a subheading for each of the following items.

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protections for Human Subjects - Section 4.1 - 4.1.4

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

If the research involves collaborating sites, provide the information identified above for each participating site.

Scenario C: Human Subjects Research Claiming Exemption 1, 2, 3, 4, 5, or 6

Criteria

Human Subjects Research	Yes
Exemption Claimed	1, 2, 3, 4, 5, or 6
Clinical Trial	Yes or No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct. The exemptions appear in Part I, Section 3, Definitions.

Although the research may be exempt from the DHHS regulatory requirements, it is still research involving human subjects and the application must follow the instructions that are identified for each of the following topics and provide the information that is requested.

In the proposal narrative, create a heading entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research falls under Exemption(s) … .”

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Justification for Claimed Exemption(s):

In this section, identify which exemption(s) (1, 2, 3, 4*, 5, or 6) you are claiming. Justify why the research meets the criteria for the exemption(s) that you have claimed.

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan – Section 4.1.5, and address the ClinicalTrials.gov requirements if applicable – Section 4.1.6.

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

*NOTE: If all the proposed research meets the criteria for Exemption 4, then the requirements for inclusion of women and minorities, targeted/planned enrollment table, and inclusion of children, do not need to be addressed.

Scenario D: Delayed-Onset Human Subjects Research

Criteria

Human Subjects Research	Yes
Exemption	Yes or No
Clinical Trial	Yes or No
NIH-Defined Phase III Clinical Trial	Yes or No

Instructions and Required Information

In rare situations, proposals are submitted with the knowledge that human subjects will be involved during the period of support, but plans are so indefinite that it is not possible to describe the involvement of human subjects in the proposal. The kinds of activities that lack definite plans are often institutional awards where the selection of specific projects is the institution's responsibility, research training grants, and projects in which the involvement of human subjects depends upon completion of instruments, animal studies, or purification of compounds.

If the involvement of human subjects is indefinite, create a heading entitled “Protection of Human Subjects” and provide a detailed explanation why it is not possible to develop definite plans at this time. The explanation should be specific and directly related to the Specific Aims in the proposal. If the involvement of human subjects depends upon information that is not presently available (e.g., completion of instruments, animal studies, purification of compounds), be explicit about the information and the factors affecting the availability of the information. Describe the information that will be necessary in order to develop definite plans for the involvement of human subjects, why that information is not currently available, and when the information is expected to become available during the course of the project.

If an award is made, prior to the involvement of human subjects the grantee must submit to the NIH awarding office for prior approval either (1) detailed information as required in the Research Plan, Protection of Human

Subjects (addressing risks to the subjects, adequacy of protection against risks, potential benefits of the proposed research, importance of the knowledge to be gained, and data and safety monitoring plan if applicable) and certification of IRB approval, OR (2) if all of the research meets the criteria for one or more exemptions, identification of which exemption(s) is/are applicable to the research, and a justification for the exemption with sufficient information about the involvement of human subjects to allow a determination that the claimed exemption is appropriate. If the research is not exempt, the request for prior approval must also address the inclusion of women and minorities, the inclusion of children, and provide completed targeted/planned enrollment tables as required in the Research Plan.

Under no circumstance may human subjects be involved in non-exempt research until approval is granted by the awarding entity, and certification of IRB approval has been accepted by the agency.

In the proposal narrative, create a section entitled Protection of Human Subjects and a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and EITHER provide as much of the information that is requested as possible; OR describe why it is not possible to provide the information due to delayed-onset of human subjects research:

Protection of Human Subjects - Section 4.1 - 4.1.4

If the research will include a clinical trial, include a Data and Safety Monitoring Plan - Section 4.1.5, and address the ClinicalTrials.gov requirements if applicable – Section 4.1.6.

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

Scenario E: Clinical Trial

Criteria

Human Subjects Research	Yes
Exemption	Yes or No
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

In the proposal narrative, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research meets the definition of a clinical trial.” (See definition of "clinical trial" in Part I.) Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - Section 4.1 - 4.1.6

Inclusion of Women and Minorities - Section 4.2

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

If the research involves collaborating sites, provide the information identified above for each participating site.

Scenario F: NIH Defined Phase III Clinical Trial

Criteria

Human Subjects Research:	Yes
Exempt:	No
Clinical Trial:	Yes
NIH-Defined Phase III Clinical Trial:	Yes

Instructions and Required Information

In the proposal narrative, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research involves an NIH-Defined Phase III Clinical Trial.” (See "NIH defined Phase III Clinical Trial" in Definitions.)

Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - Section 4.1 - 4.1.6

Inclusion of Women and Minorities - Section 4.2

Additional Instructions and Requirements when NIH-Defined Phase III Clinical Trials are Proposed - Section 4.2.1

Targeted/Planned Enrollment Table - Section 4.3

Inclusion of Children - Section 4.4

If the research involves collaborating sites, provide the information identified above for each participating site.

4. INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your proposal narrative, **create a section entitled “Human Subjects.”** Although no specific page limitation applies to this section of the proposal, be succinct. Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the protection of human subjects. DHHS regulations and policies governing human subjects research are described and referenced in Section 5 below. **Use subheadings** to address the issues listed under items 4.1-4.4 below. If your research includes a clinical trial, include a subheading "Data and Safety Monitoring Plan" and follow the instructions in 4.2 below. If your research includes an NIH-Defined Phase III Clinical Trial, follow the additional instructions in 4.2.1 below.

4.1 PROTECTION OF HUMAN SUBJECTS

4.1.1Risks to Human Subjects

a. ***Human Subjects Involvement and Characteristics***

- Describe the proposed involvement of human subjects in the work outlined in the Human Subjects Research section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

- Identify the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research.

b. ***Sources of Materials***

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for the proposed research project.

c. ***Potential Risks***

- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

4.1.2Adequacy of Protection Against Risks

a. ***Recruitment and Informed Consent***

- Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. ***Protections Against Risk***

- Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:

  Additional Protections for Pregnant Women, Human Fetuses and Neonates:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb

  Additional Protections for Prisoners:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc
  OHRP Subpart C Guidance: http://www.hhs.gov/ohrp/policy/index.html#prisoners

  Additional Protections for Children:
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd
  OHRP Subpart D Guidance: http://www.hhs.gov/ohrp/children/

- Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of the research and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

4.1.3Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

4.1.4Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

4.1.5Data and Safety Monitoring Plan

The NIH Data and Safety Monitoring Plan Policy is described and referenced in Section 5.3.

- If the research includes a clinical trial, create a heading entitled "Data and Safety Monitoring Plan."
- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov/) and also see the following websites for more information related to IND and IDE requirements:
  http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
  http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)
- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:
  a. PD/PI (required)
  b. Institutional Review Board (IRB) (required)
  c. Independent individual/safety officer
  d. Designated medical monitor
  e. Internal Committee or Board with explicit guidelines
  f. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html). For additional guidance on creating this Plan, see the above reference.

4.1.6ClinicalTrials.gov Requirements

Public Law 110-85 mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf)).

NIH encourages registration of ALL trials whether required under the law or not.

Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Website (http://prsinfo.clinicaltrials.gov/). A unique identifier called an NCT number will be generated during the registration process.

For new and renewal (competing) applications that include ongoing clinical trials which require registration and results reporting, provide the NCT number/s, Brief Title/s (as defined by ClinicalTrials.gov, see http://prsinfo.clinicaltrials.gov/), and the identity of the responsible party (or parties) in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov. The entity responsible for registering is the “responsible party.” The statute defines the responsible party as:

(1) the sponsor of the clinical trial (as defined in 21 C.F.R. 50.3) (http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqtr/pdf/21cfr50.3.pdf), or

(2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that “the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements” for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

If a new applicable trial is proposed, under the heading ClinicalTrials.gov include a statement that the application includes a trial which requires registration in ClinicalTrials.gov. The signature on the application of the Authorized Organizational Representative assures compliance for the registration of any such trial.

4.2 INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the “Protection of Human Subjects" section. Although no specific page limitation applies to this section of the proposal, be succinct. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced in Section 5.6.

Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the protection of human subjects.

In this section of the Research Plan, address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below in 4.3.) If using existing specimens and/or data without access to information on the

distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion is inappropriate (item 3 below). Alternatively, describe the women and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table in this section.

2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).
4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. ***One gender:***

1. One gender is excluded from the study because:
   - inclusion of these individuals would be inappropriate with respect to their health;
   - the research question addressed is relevant to only one gender;
   - evidence from prior research strongly demonstrates no difference between genders; or
   - sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.
2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. ***Minority groups or subgroups:***

1. Some or all minority groups or subgroups are excluded from the study because:
   - inclusion of these individuals would be inappropriate with respect to their health;
   - the research question addressed is relevant to only one racial or ethnic group;
   - evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;
   - a single minority group study is proposed to fill a research gap; or
   - sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.
2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
   - the size of the study;
   - the relevant characteristics of the disease, disorder or condition; or
   - the feasibility of making a collaboration or consortium or other arrangements to include representation.

3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the research.

4.2.1Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether clinically important sex/gender and/or race/ethnicity differences are expected from the intervention effect. The discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. The discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, *or*
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), *or*
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

4.3 INSTRUCTIONS FOR COMPLETING THE TARGETED/PLANNED ENROLLMENT TABLES FOR REPORTING RACE AND ETHNICITY DATA FOR SUBJECTS IN CLINICAL RESEARCH

The NIH Policy on Reporting Race and Ethnicity Data for Subjects in Clinical Research is described and referenced in Section 5.8.

A. New Proposals

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on the Office of Management and Budget (OMB) reporting standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

When reporting these data in the aggregate, investigators should report: (a) the number of research participants in each ethnic category; (b) the number of research participants who selected only one category for each of the five racial categories; (c) the total number of research participants who selected multiple racial categories reported as the “number selecting more than one race,” and (d) the number of research participants in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed data should be compiled in a way that they can be reported using the required categories.

Instructions for Completing Targeted/Planned Enrollment Table

(http://grants.nih.gov/grants/funding/424/SF424R-R_enrollment.doc)

Provide the study title.

The "Total Planned Enrollment" means the number of subjects that are expected to be enrolled in the study, consistent with the definition in ClinicalTrials.gov.

The "Total Planned Enrollment" will be reported in two ways in the table: by "Ethnic Category" and by "Racial Categories."

"Ethnic Category": Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

"Racial Categories": Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is an ethnic, not a racial, category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender using the Targeted/Planned Enrollment Table. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories.

If Data Collection is Ongoing, Such that New Human Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators should report ethnicity/race and sex/gender sample composition using the Inclusion Enrollment Report.

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators should use the Inclusion Enrollment Report.

Research Conducted at Foreign Sites:

If proposed studies involve a foreign site, investigators are encouraged to design culturally sensitive and appropriate data collection instruments that allow research participants to self-identify their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the OMB-required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables that describe research in foreign sites, investigators should asterisk and footnote the table indicating that data includes research participants in foreign sites. If the aggregated data only includes participants in foreign research sites, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign sites, the investigator should complete two separate tables – one for domestic and another for foreign participants.

B. Progress Reports

The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) must be used for reporting accrual data to the NIH. In annual progress reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on the Inclusion Enrollment Report, and update the Targeted/Planned Enrollment Table as needed.

4.4 INCLUSION OF CHILDREN

The NIH Policy on Inclusion of Children is referenced and described in Section 5.7. Instructions for this item under the "Human Subjects" heading of the Research Plan are as follows:

- Create a section entitled "Inclusion of Children" and place it immediately following the Targeted/Planned Enrollment Table.
- For the purpose of implementing these guidelines, a *child* is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).
- Provide either a description of the plans to include children, or, if children will be excluded from the proposed research, application, or proposal, present an acceptable justification for the exclusion (see below).
- If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the research project.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR Part 46 Subpart D (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd)) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

Justifications for Exclusion of Children

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section. It is expected that children will be included in all clinical research unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is not relevant to children.
2. There are laws or regulations barring the inclusion of children in the research.
3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
4. A separate, age-specific study in children is warranted and preferable. Examples include:
   a. The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a

particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or

b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or

c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

6. Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).

7. Other special cases can be justified by the investigator and found acceptable to the review group and the Institute Director.

5. HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes DHHS regulations for the protection of human subjects and the following NIH policies related to human subjects research.

5.1 PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (DHHS) regulations for the protection of human subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. The regulations stipulate that the awardee organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in DHHS-supported research activities. The regulations require that offeror organizations proposing to involve human subjects in nonexempt research hold a Federal-wide Assurance (FWA) with the Office for Human Research Protections (OHRP), and establish appropriate policies and procedures for the protection of human subjects. These regulations, 45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm), Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD; telephone: 1-866-447-4777 (toll-free) or (240) 453-6900; email: ohrp@osophs.dhhs.gov.

Nonexempt research involving human subjects may only be conducted under a DHHS award if the organization is operating in accord with an approved FWA and provides verification that an Institutional Review Board (IRB) that is registered under the specific FWA has reviewed and approved the proposed activity in accordance with the DHHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the DHHS regulations. Foreign offeror organizations must also comply with the provisions of the regulations unless a determination of equivalent protections is made in accord with 45 CFR 46.101(h).

Under DHHS regulations to protect human subjects, certain research areas are exempt. However, if an offeror makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or the return of the application without review. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. With the exception of research projects that meet the criteria for Exemption 4, studies that are exempt from the human subjects regulatory requirements must still address the inclusion of women, minorities and children in the study design.

Regulations of the Food and Drug Administration (21 CFR 50, 21 CFR 56) generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Additional information on FDA regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm. If work falls under FDA's regulatory requirements, the grantee must follow both DHHS and FDA human subject protection regulations.

The *National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* apply to all projects (NIH-funded and non NIH-funded) involving recombinant DNA molecules that are conducted at or sponsored by an institution that receives NIH support for recombinant DNA research. As defined by the *NIH Guidelines*, recombinant DNA molecules are either: (1) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (2) DNA molecules that result from the replication of those described in (1). The *NIH Guidelines* set forth principles and standards for safe and ethical conduct of recombinant DNA research and apply to both basic and clinical research studies. The *NIH Guidelines* should be carefully reviewed and implemented to ensure that proper biosafety and containment practices are employed for all projects involving recombinant DNA research, including review by an Institutional Biosafety Committee that meets the requirements of the *NIH Guidelines*. Further, the *NIH Guidelines* include special review and reporting requirements for the conduct of human gene transfer studies (under Appendix M). Failure to comply with the *NIH Guidelines* may result in suspension, limitation, or termination of NIH funds for recombinant DNA research at the organization or a requirement for NIH prior approval of any or all recombinant DNA projects at the organization. A copy of the *NIH Guidelines* is posted at the following URL: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html and may be obtained from the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892, 301-496-9838.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens, and medical information. Research involving the collection or study of existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered “research involving human subjects.” The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions to help investigators understand how these federal requirements apply to their research. See http://grants.nih.gov/grants/policy/hs/index.htm.

The DHHS regulations require the NIH to evaluate all proposals involving human subjects (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.120). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the proposal, or enter into negotiations to develop an approvable one.

5.2 VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners, or children, must follow the provisions of the regulations in Subparts B, C, and D of 45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm), respectively. The subparts describe the additional protections required for conducting research involving these populations. Relevant information may be obtained at the OHRP website (http://www.hhs.gov/ohrp/policy/index.html).

REMINDER: DHHS regulations at 45 CFR Part 46, Subpart C (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc) describe requirements for additional protections for research involving prisoners as subjects *or* individuals who become prisoners after the research has started. Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm for complete instructions.

Exemptions 1-6 do **not** apply to research involving prisoners or subjects who become prisoners (see Subpart C (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc)). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#

subpartd)), Exemption 2 can only be used for research involving educational testing or observations of public behavior when the investigator(s) do not participate in the activities being observed.

5.3 DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. Prior to the accrual of human subjects, a detailed data and safety monitoring plan must be submitted to the offeror's IRB and to the funding entity for approval. Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other appropriate offices or agencies. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm). NIH policy specifically requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

5.4 IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of a proposal. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html.

Following NIH peer review, the offeror organization will be notified of the need for review and approval of the proposed research by an IRB that is registered with OHRP. See http://www.hhs.gov/ohrp/ to register an IRB. Certification of IRB approval must be sent to the Grants Management Office identified in the notice requesting documentation. Certification of IRB review and approval must include: the PHS SBIR proposal number, title of the project, name of the program director /principal investigator, date of IRB approval, and appropriate signatures. Grantees may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule)" (OMB Form No. 0990-0263 http://www.hhs.gov/ohrp/humansubjects/assurance/OF310.rtf) to meet this requirement.

The OHRP has determined that an institution is automatically considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. See http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm. All institutions engaged in human subjects research must obtain a Federal Wide Assurance (FWA) from OHRP. Instructions for applying for a Federal Wide Assurance (FWA) are available from the OHRP website at http://www.hhs.gov/ohrp/assurances/assurances_index.html.

Any modifications to the Research Plan in the proposal, required by either NIH or by the IRB, must be submitted with follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the PD/PI and the offeror organization to submit the follow-up documentation.

If more than a year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

5.5 REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified in PHS applications as Senior/key Personnel who will be involved in the design or conduct of human subjects research, before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following notices http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html, and Frequently Asked Questions at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, offerors will be required to provide a description of education completed in the protection of human subjects for all Senior/key Personnel involved in the design or conduct of human subjects research. Although NIH does not endorse specific programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp for computer-based training

developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

5.6 NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

NIH policy requires that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant IC Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study. The Research Plan should describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.7 NIH POLICY ON INCLUSION OF CHILDREN

Research involving children (see definition of "child") must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from http://grants.nih.gov/grants/funding/children/children.htm.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the proposal must present an acceptable justification for the exclusion.

The involvement of children as subjects in research must be in compliance with all applicable subparts of 45 CFR Part 46 (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm) as well as with other pertinent Federal laws and regulations.

IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

5.8 NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (http://www.whitehouse.gov/omb/fedreg/ombdir15.html) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH). The standards were revised in 1997 and include two ethnic categories (Hispanic or Latino and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). Reports of data on race and ethnicity shall use these categories. The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study.

Guidance on Collecting Race and Ethnicity Data from Human Subjects

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category. An example of a format for collecting information from study subjects in the US that meets the OMB requirements can be found in the Ethnic Origin and Race section of the Personal Data Form Page http://grants.nih.gov/grants/funding/phs398/phs398.html in the PHS 398.

See NIH Policy on Inclusion of Women and Minorities and http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.9 RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research on the transplantation of human fetal tissue is conducted, the offeror organization will make available, for audit by the Secretary, DHHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure DHHS access to those records, if maintained by an entity other than the offeror organization.

5.10 RESEARCH USING HUMAN EMBRYONIC STEM CELLS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research using human embryonic stem cells is proposed, the offeror organization will be in compliance with the "Notice of Extended Receipt Date and Supplemental Information Guidance for Applications Requesting Funding that Proposes Research with Human Embryonic Stem Cells" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html). See http://stemcells.nih.gov/index.asp for additional information on stem cells, and http://stemcells.nih.gov/policy/guidelines.asp for Federal policy statements and guidelines on federally funded stem cell research.

5.11 CLINICALTRIALS.GOV REQUIREMENTS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if the research is an applicable clinical trial under Public Law 110-85, the offeror organization will be in compliance with the registration and reporting requirements of Public Law 110-85, if applicable (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). The law, enacted 09/27/2007, amends the Public Health Service Act to expand the scope of clinical trials that must be registered in ClinicalTrials.gov. It also increases the number of registration fields that must be submitted, requires certain results information to be included, and sets penalties for noncompliance.

The trials that must be registered are called "applicable clinical trials." Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. NIH encourages registration of ALL trials whether required under the law or not.

For additional information see NIH Guide Notices at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html and http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-023.html.